AUSTRALASIAN ANNALS OF MEDICINE

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AUSTRALASIAN ANNALS OF MEDICINE

VOLUME 6 FEBRUARY, 1957 NUMBER 1

OBSERVATIONS ON THYROID STUDIES IN NEW ZEALAND[1]

SIR CHARLES E. HERCUS[2]

From the University of Otago, Dunedin

SUMMARY

Thirty-five years ago we commenced a study on the causation and prevention of thyroid disease in this country.

The first reports of endemic goitre were made in 1888, and in 1920 the relationship to low iodine environment was reported. After some preliminary failures prophylaxis with iodized salt was successful in 1940. The goitrogenic factor in certain foodstuffs was studied in 1928 and subsequently, and this work was the forerunner of the therapeutic use of thiouracil.

Currently we are studying thyroid function by means of radioactive iodine, and experience in its use in diagnosis and treatment is presented.

While progress has been made, more questions have been raised than answered. It is indeed true that " Knowledge is proud that he knows so much, while Wisdom is humble that he knows no more ".

THE New Zealand Fellows and Members of The Royal Australasian College of Physicians welcome to this our capital city so many Australian Fellows and Members.

I have been asked to give a brief review of the goitre situation in New Zealand before presenting some recent work on the use of radioactive iodine in the assessment of thyroid function. Unlike Australia, one of the oldest parts of our planet, New Zealand is young and possibly in consequence somewhat unstable. Its soils also are immature, lacking certain important trace elements. In contrast to Australia, man and indeed all the mammalia if we except two species of bats, are but recent arrivals to these islands. Palæolithic man probably walked to Australia by land bridges from southern Asia via New Guinea and Torres Strait some fifty million years ago. There were no land bridges to New Zealand. The crossing of the Pacific Ocean was the pre-requisite to man's arrival—no easy task.

While there is evidence that the first human inhabitants arrived about the fifth century of our era, their advent being more by accident than design, the main migration of the Polynesians took place about 1350. These " Vikings of the Sunrise ", as Buck called them, were more advanced than the Stone Age man of Australia; for, though they still depended on stone for their weapons and tools, and though the art of writing and of the potter had escaped them, they had learnt to cultivate the sweet potato and to domesticate the dog and apparently the rat, both of which mammals arrived with them. New Zealand, though much colder than their home lands, must have appeared very favourable for human occupation. Situated wholly within the temperate zone, well watered and forested, New Zealand had no predatory mammals, no snakes and ample first class protein in the all-embracing ocean and in the forest full of birds, many wingless and easily killed.

As long as the Maori lived close to our extensive coast line and included much sea food in his dietary, tradition tells us that his health was excellent. When Captain Cook first visited this country in 1769 he stated in his diary that " these people enjoyed perfect and uninterrupted health in all our visits to their towns where young and old, men and

[1] Read at the annual meeting of The Royal Australasian College of Physicians in Wellington, New Zealand, March, 1956.

[2] Professor of Preventive and Social Medicine.

women crowded about us, we never saw a single person who appeared to have any bodily complaint, nor among the numbers that we have seen naked did we perceive the slightest eruption upon the skin or any marks that any eruption had left behind . . . A further proof that human nature is here untainted with disease is the great number of old men that we saw, many of whom by the loss of their hair and teeth appeared to be very ancient, yet none of them were decrepit and though not equal to the young in muscular strength were not a bit behind them in cheerfulness and vivacity."

When, however, internecine strife drove some of the tribes away from the sea and their food stuffs had to come entirely from the soil, the consequences of our geological heritage began to become manifest. The whole country had been glaciated during the ice periods, and much of the soil deposited by glacial action was deficient in iodine. It is impossible to state when endemic goitre first appeared among these inland-dwelling Maoris, but their oral tradition records quite definitely that goitre preceded the European settlement of the early part of the nineteenth century. The full significance of this geological situation did not become evident, however, until the European settlement had been established for some years. It was not until 1888 that the first contribution to medical literature on the widespread incidence of goitre in Canterbury was published by Hacon (1888). In 1910 Professor Colquhoun reported that goitre was widespread throughout the country (Colquhoun, 1910).

Extensive field and laboratory studies in the 1920's (Hercus *et alii*, 1925) revealed a direct relationship between the incidence of endemic goitre and low iodine environment. Owing to the inherent difficulties in estimating minute quantities of iodine in foodstuffs it was found that the most delicate and accurate index of iodine ingestion was the measurement of the twenty-four-hour excretion of iodine in the urine. Iodized salt to make up the deficiency was introduced as a voluntary measure in 1924; but as the level of supplementation was only one part of potassium or sodium iodide per 250,000 parts of salt, which even when used for both table and culinary purposes provided not more than 30 microgrammes of iodine daily, the measure was ineffective. It was not until after 1940, when the level of iodine in domestic salt was raised to one part of sodium or potassium iodide to 20,000 parts of salt, that a notable decline in the incidence of thyroid enlargement first became apparent. Where this salt has been used regularly for both table and cooking purposes the endemic has disappeared.

While not peculiar to New Zealand, the thyroid situation here was further complicated by the presence of various goitre-inducing substances first discovered in cabbage (Chesney *et alii*, 1928). Throughout the 1930's we studied many of these goitrogenic substances occurring naturally in New Zealand foodstuffs. In 1933 we demonstrated goitrogenic activity in the roots and seeds of various members of the brassica species. Though we were unable to isolate the active agent, later achieved in 1949 (Astwood *et alii*, 1949), Kennedy in 1942 reported that thiourea was goitrogenic and

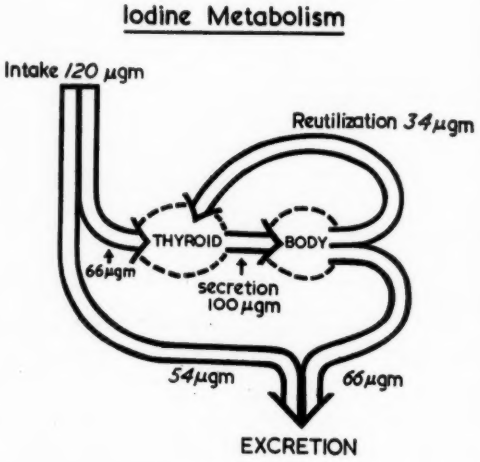

FIGURE I

Iodine metabolism in a young adult patient in iodine equilibrium

suggested its use in the treatment of hyperthyroidism (Kennedy, 1942). At the same time, and quite independently, McKenzie, McKenzie and McCollum (1941) described the goitrogenic action of sulphaguanidine, and Richter and Clisby (1942) described a similar action for phenylthiourea. Allylthiourea, synthesized in the chemistry department of this University, was first used here for the treatment of hyperthyroidism in October, 1943, shortly before the appearance of Astwood's (1943) contribution to the use of these drugs as inhibitors of thyroid function. Our subsequent experience with the thiourea group of drugs in the treatment of hyperthyroidism has been reported elsewhere, but it differs in no substantial way from general experience.

In 1950 the availability in New Zealand of the radioactive isotope of iodine, I^{131}, enabled a

series of studies to be undertaken on the pathways of iodine metabolism and the assessment of thyroid function and the use of I^{131} in the treatment of toxic and malignant goitre. One object of this communication is to submit suggestions for a standard procedure designed to measure thyroid function. The results are based on several hundred individual studies of euthyroid, hyperthyroid and hypothyroid individuals.

Before discussing the proposed standard method I propose to summarize our present knowledge or half knowledge of the intermediate metabolism of the thyroid hormone.

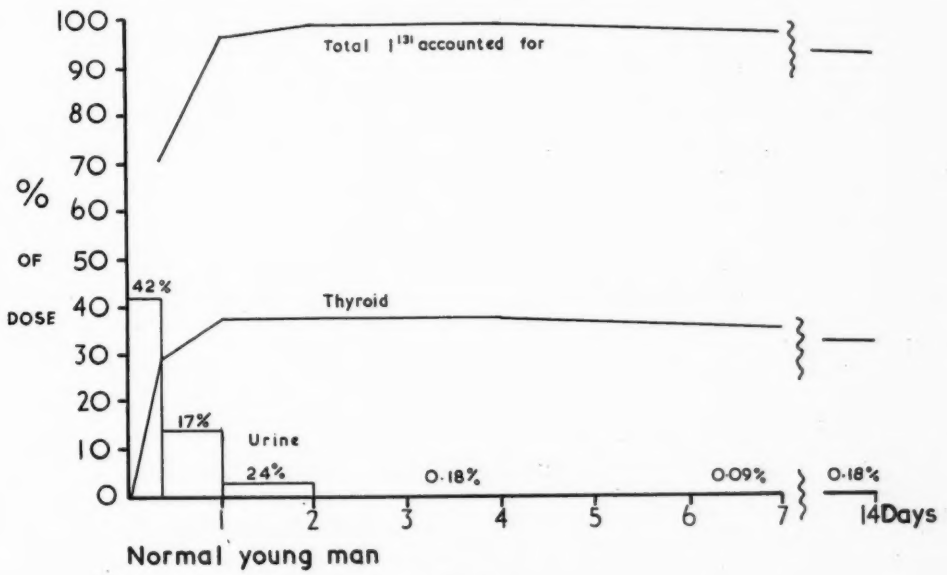

FIGURE II

Thyroid uptake and urinary excretion of I^{131} after an oral dose of 15 microcuries, in a normal subject

The introduction of radioactive iodine as an in-vivo and in-vitro tracer has permitted the filling in of certain details in the metabolic story, though it is remarkable how sound had been the conclusions of earlier workers using ordinary chemical methods. Figure I outlines the present state of knowledge of iodine metabolism in a young, healthy adult in iodine equilibrium at a daily intake of 120 microgrammes to whom a test dose of I^{131} has been given. It will be seen that approximately half of the iodide is excreted by the kidney, while the remainder is taken up by the cells of the thyroid follicle. Here it is incorporated in the thyroglobulin, which contains thyroxine and triiodothyronine together with other iodinated compounds, the ultimate concentration of iodine being some 10,000 times the plasma level. Under the influence of the thyrotrophic hormone of the pituitary and according to the demands of the body some 100 microgrammes daily of iodine are liberated into the blood-stream; there it unites with the plasma protein, passing to all the cells of the body, in what manner and for what purpose remaining still unknown. The exact composition of this 100 microgrammes of iodine is not known, but at least 80% of it is thyroxine. Ultimately, iodide is liberated from the hormone molecule; approximately two-thirds of this is excreted by the kidney, and one-third rejoins the extrathyroidal pool. This amazing chemical performance calls to mind Sherrington's masterly prose when he described the metabolic activity in a single cell: "A scene of energy-cycles, suites of oxidation and reduction, concatenated ferment-actions. It is like a magic hive the walls of whose chambered spongework are shifting veils of ordered molecules and rend and renew as operations rise and cease. A world of surfaces and streams. We seem to watch battalions of specific catalysts, like Maxwell's 'demons', lined up, each waiting, stop-watch in hand, for its moment to

play the part assigned to it, a step in one or other great thousand-linked chain process. Yet each and every step is understandable chemistry. The cell has proved to be a perfect swarm of catalysts, or of trains of catalysts, each a link in a serial suite of chemical action."

The method used in Dunedin for routine assessment of thyroid activity is as follows. An amount of 15 microcuries of I^{131} made up to 50 millilitres with a dilute solution of sodium carbonate is drunk through a straw from a polythene drinking vessel. The amount of I^{131} accumulated in the thyroid is measured eight hours later and again in forty-eight hours. At the same time, as a check on the thyroid measurement, the forty-eight-hour urinary excretion of I^{131} is also measured. Adams and Purves (1956) have published details of the method. The actual measurements in three cases are shown in the following figures.

In Figure II, in which the subject was a normal individual, it will be seen that the gland accumulates the tracer I^{131} slowly. The thyroid I^{131} content reaches a maximum at about forty-eight hours and thereafter falls at a slow rate. Urinary secretion is relatively high. Figure III shows the findings in a case of primary Graves' disease, the thyroid uptake being more rapid with a much higher maximum value followed by a more rapid fall. The pattern of uptake and release in secondary Graves' disease is similar. In Figure IV, which relates to a case of hypothyroidism, the thyroid uptake is low, the maximum being 4%. Most of the remainder of the I^{131} was excreted by the kidney, 84% appearing in the first forty-eight hours.

From our experience we believe that if these three measurements, of thyroid uptake at eight and forty-eight hours and forty-eight-hour urinary excretion, are within the normal range, there is no hyperthyroidism, provided that the patient has not been ingesting large doses of iodine. This is of considerable help to the clinician when confronted with a doubtful case of thyrotoxicosis. Unfortunately the converse is not true. Measurements outside the normal range may be due to causes other than hyperthyroidism. A deficiency of iodine in the diet will increase the rate of thyroid uptake and secretion. If iodine deficiency is suspected, the tracer test should be repeated after carrying out one of the following procedures. In one the patient is given a high iodine intake (about one milligramme daily) for a period of three weeks, and one week later the I^{131} tracer test is repeated. If the result is now normal, the previous overactivity was the result of iodine lack. In the other, the patient is treated with thyroxine (0·6 milligramme daily) for a week before repeating the tracer test. In the absence of hyperthyroidism, thyroid uptake is depressed and the secretion rate almost completely inhibited (Greer and Smith, 1954). In these patients the original increased thyroid uptake was due to an elevated blood thyrotrophin level consequent on the iodine deficiency. The administration of thyroxine depresses the elevated blood thyrotrophin level, thus lowering the thyroid uptake. The normal regulating

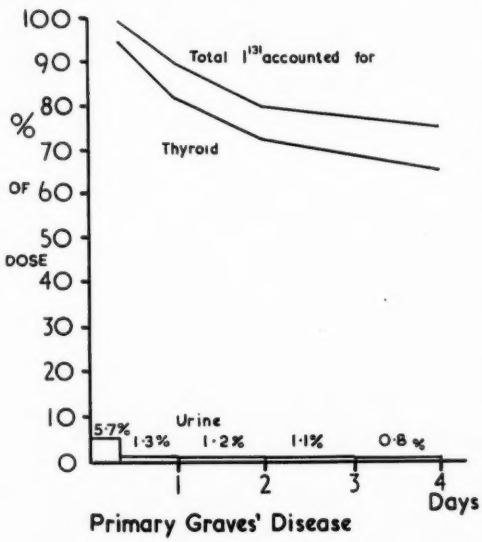

FIGURE III

Thyroid uptake and urinary excretion of I^{131} after an oral dose of 15 microcuries in a patient with primary Graves' disease

mechanism is working smoothly. In thyrotoxic patients, however, there is little effect on the uptake or the secretion rate. The homœostatic mechanism is disturbed. More than this we cannot say. The solution to the problem of the ætiology of Graves' disease, despite a hundred years of research, still evades us. We know nothing as to how the nervous system influences the hormonal situation and *vice versa*.

Whilst the administration of I^{131} in therapeutic doses has proved an effective method of treating thyrotoxicosis, we think that it should be used conservatively because of possible undesirable radiation effects. Therapeutic doses of I^{131} may produce mutations in

the sex cells, leading to congenital defects in future generations, and may also produce subsequent malignancy. Therefore, we use antithyroid drugs or surgery wherever possible, except in elderly patients, past the reproduction age, whose life expectancy is not more than twenty years.

The rationale of the procedure is to destroy *in situ* cells of thyroid origin, whether normal, hyperplastic or malignant, using doses of I^{131} a thousand times greater than are used for the tracer testing. The unit is millicuries as opposed to microcuries. The I^{131} is trapped by the thyroid cells as before and passes into the colloid. Beta particles are emitted from the I^{131} and strike all cells within a radius of two millimetres. The result is to produce disorganization and ultimate death of the cells exposed. It is simply an example of local irradiation. There is no specific chemical action, as is the case with the antithyroid drugs. The whole process is dependent upon the uptake and retention for a sufficient time of the I^{131}. In the case of diffuse hyperplastic glands a single dose of five to ten millicuries will give a high percentage of cures. With nodular glands on the other hand, where some nodules are active and others inactive, it is necessary to give doses of smaller size more frequently or to give a much larger single dose of up to 50 millicuries, which leaves the residual gland able to maintain the patient in a euthyroid state.

A certain minority of malignant thyroid tumours have a well developed acinar structure, and the cells take up I^{131} as in the normal thyroid gland. In such cases a destructive effect can be secured by the use of repeated doses of 50 to 100 millicuries up to the limit of the patient's radiation toleration. As a prerequisite it is necessary to remove the functioning thyroid tissue, preferably by surgery, in order to ensure the maximum uptake in the tumour cells. In one of our cases of thyroid carcinoma with widespread pulmonary metastases, there was a striking response to the exhibition of thyroid hormone. Balme has also found exhibition of thyroxine to produce a regression in the pulmonary metastases of a case of thyroid carcinoma (Balme, 1954). It would appear that in some cases of metastasizing thyroid carcinoma the tumour flourishes only if supplied with thyrotrophic hormone. I^{131} therapy is effective in only a very small proportion of cases of thyroid carcinoma. It may be that thyroid hormone

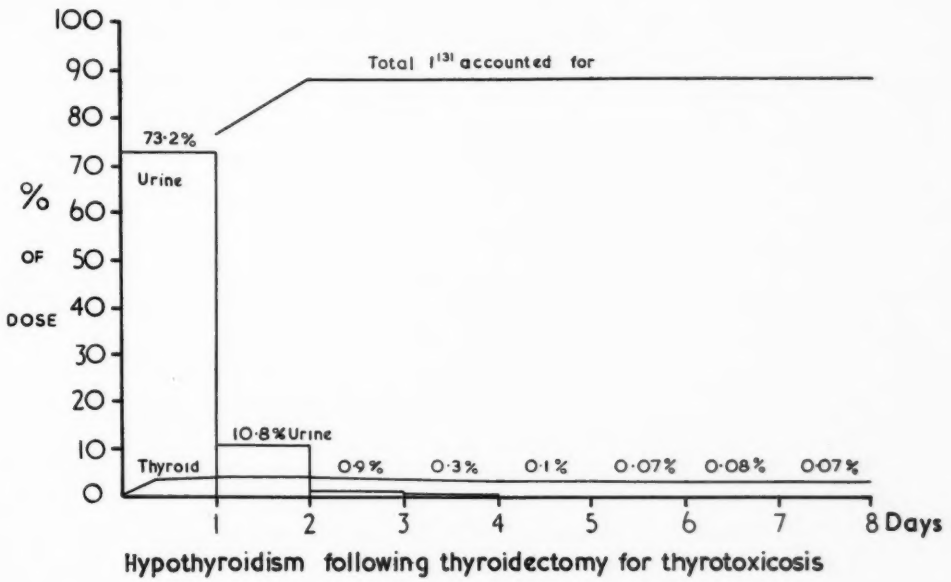

FIGURE IV

Thyroid uptake and urinary excretion of I^{131} after an oral dose of 15 microcuries in a patient with hypothyroidism

therapy will prove to be as effective as, or even more effective than I^{131} therapy. Neither, however, is likely to benefit more than a small percentage of patients with thyroid carcinoma.

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THE TREATMENT OF LITHIUM POISONING[1]

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SUMMARY

Lithium salts are valuable in treatment of psychomotor overactivity. Administered lithium is distributed throughout the total body water and intracellular lithium accumulates at the expense of potassium. Lithium appears to interfere with intracellular, potassium-dependent, metabolism.

Sporadic cases of intoxication may occur if treatment is not controlled clinically and biochemically. The symptoms are: gastro-intestinal disturbance, ataxia, urinary and fœtal incontinence, and coma. Preliminary symptoms may be insidious, and coma may develop suddenly. Treatment aims at promotion of cellular potassium uptake with release of lithium for renal excretion.

Six illustrative cases are reported.

LITHIUM SALTS are assuming a greater importance in the treatment of a number of conditions associated with psychomotor overactivity. With this increased use the incidence of lithium poisoning is increasing, particularly in patients released from the supervision of institutions experienced in the therapy and equipped for its laboratory control. Hence it is of some importance that there be a general recognition of the mode of action of the lithium ion in the body, the principles of control of therapy, the early signs of toxicity and the measures to be adopted for its treatment.

Minor grades of lithium poisoning, manifested by nausea, anorexia, loss of weight and a slightly staggering gait, are not uncommon, and can usually be treated by mere reduction or withdrawal of the medication. Their recognition is important, for untreated they may progress to a more severe form of poisoning associated with acute collapse, coma and death (Trautner *et alii*, 1955; Corcoran *et alii*, 1949). The usual sequence of events in this progression is that over a period of one or two weeks the patient has lost both weight and appetite, has experienced some nausea, and possibly displays minimal ataxia. Frequently these early symptoms and signs have passed unrecognized. Without further warning, and often within a few hours, the patient may become confused, be unable to stand, become incontinent of urine and fæces, often with polyuria, and lapse into coma. Motor disturbances are almost always to be found, including fasciculation of the muscles of the hands and face and frequently isolated jerky contractions of the limbs easily elicited by handling. Very rarely there may be choreiform movements or epileptiform convulsions. The muscles are often flaccid. The differential diagnosis from other comas of sudden onset depends upon a history of lithium treatment and a plasma lithium concentration exceeding 2·5 milliequivalents per litre. Untreated, the condition will progress within a few days to gross dehydration, oliguria or anuria, and death.

Treatment of established lithium poisoning has hitherto been unsatisfactory, being based on the supposition that as lithium intake is initially associated with a negative external sodium balance, the cessation of intake and the institution of massive sodium therapy will hasten its elution from the body (Noack and Trautner, 1951; Glesinger, 1954). Treatment along these lines would seem to be ineffectual, and there is little evidence that the excretion of lithium from the body is significantly hastened. Hanlon *et alii* (1949) were unable to demonstrate increased excretion of lithium following saline infusion. They concluded that no means are known of hastening the excretion of lithium from the body or of counteracting its toxic effects. Radomski *et alii* (1950) showed that the administration to dogs of large doses of both DOCA and adrenal corticol extract did not

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prevent or ameliorate the syndrome of lithium poisoning, and did not increase their survival time.

To be effective, treatment of lithium poisoning must result in increased lithium excretion and the restoration of ionic equilibria between the various body water compartments disturbed by their erstwhile lithium content. For this reason therapy must be based on an appreciation of the distribution of the lithium ion in the body.

FATE OF INGESTED LITHIUM

After the institution of lithium medication there is a period of some seven days during which there is a positive balance and a gradual increase in the total lithium content of the body. Over this period lithium intake exceeds lithium excretion (Trautner *et alii*, 1955), but thereafter during continued administration at the same dosage there is in most cases a precise balance between intake and excretion. If the total body water is assumed to be 70% of body weight, the retained lithium, if evenly distributed throughout this water, would be present at the concentration actually found in plasma. Radomski (1950) has shown that lithium is evenly distributed over total body water, while Foulks *et alii* (1952) have actually demonstrated an intracellular lithium accumulation against a concentration gradient. In this respect lithium behaves in the same fashion as potassium in the body, and its infusion furnishes a stimulus to the renal secretion of potassium.

The body's lithium content may remain stable for many months, but this stability depends upon a continuing equivalence of intake and excretion. Increased lithium intake, or decreased excretion, must result in a resetting of the equilibrium with an increase in the total body content. In some cases (Trautner *et alii*, 1955) the minimum effective therapeutic dosage is such that there is no great margin between the total body content for adequate symptomatic control and that for the precipitation of poisoning. Even minor decreases in excretion, such as may be associated with increased environmental temperature or intercurrent infection, may be sufficient to precipitate lithium poisoning.

As the greater part of the lithium in the body is intracellular, in the event of lithium poisoning it is a first essential in treatment that measures be adopted to promote cellular release. Intracellular lithium would seem to accumulate at the expense of potassium, and the promotion of cellular potassium uptake should result in lithium release. It is only after it has been displaced from its intracellular environment that the lithium is available for renal excretion.

PRINCIPLES OF TREATMENT

The principles adopted in the treatment of lithium intoxication are all directed towards its rapid elimination from the body, and more especially the rapid reduction of the large intracellular fraction. These principles may be briefly set out as follows:

1. Cessation of intake. As soon as the earliest evidence of lithium poisoning appears, its administration is suspended.

2. Promotion of diuresis. One of the earliest signs of lithium poisoning is an increase in urinary volume, and it is essential in treatment that this increased urinary output be maintained. Untreated, a patient with lithium poisoning may quite rapidly show evidence of dehydration, with an associated gradual reduction in urinary volume. Hence it is of prime importance that fluid intake, either oral or if necessary intravenous, be maintained at a high level so as to ensure the continuation of the initial diuresis and to prevent the occurrence of dehydration.

3. Promotion of cellular potassium uptake. In our experience serum potassium levels in cases of established lithium poisoning have been normal or low. This is the case even when there is considerable dehydration, with a consequent reduction in extracellular fluid volume and a presumed intracellular potassium depletion commensurate with the intracellular lithium content. Hence it is evident that normal water and ionic relationships can be restored only after the provision of an amount of potassium adequate to correct the total body deficit. Potassium may be given either orally, in early cases of poisoning, or by infusion, and dramatic clinical improvement has been noted to follow its provision.

4. The provision of calories. Established lithium poisoning is associated with a greater or lesser degree of starvation ketosis, and it is essential in treatment that this be corrected. Glucose fluids given orally, or intravenous glucose infusions to provide not less than 200 grammes of glucose in twenty-four hours, are necessary to correct the ketosis. It is usually advisable at the same time to cover the glucose administration with insulin. As well as correcting the ketosis, this therapy promotes the cellular uptake of potassium and consequently the cellular release of lithium.

5. Correction of acidosis. The provision of adequate calories in the form of glucose is usually sufficient to correct mild starvation ketosis, but in severe cases it may be necessary initially to infuse a sodium bicarbonate solution. Care should be taken that the quantity infused be kept sufficiently small to avoid a later addition alkalosis following the correction of the ketonæmia with glucose and insulin.

The method of application of these various principles of treatment is demonstrated in the following clinical histories.

REPORTS OF CASES

CASE I.—R.C., a male patient, aged twenty-nine years, was brought to hospital grossly confused, incontinent of urine and fæces and ataxic. He showed twitches of the small muscles of the hands and face and occasional muscular jerks of the arms and legs. The only history available was that he had been receiving lithium treatment for chronic maniacal excitement and that he had lately lost much weight. His skin was dry and loose, the peripheral circulation was poor and the extremities were cold. His blood pressure was 110 millimetres of mercury, systolic, and 70 millimetres, diastolic, and his pulse rate was 78 per minute. Respiration was irregular and laboured, and his rectal temperature was 98·8° F. The plasma electrolyte concentrations in milliequivalents per litre were as follows: sodium, 145; potassium, 3·9; lithium, 3·6.

Treatment was started with an intravenous infusion of a solution containing 5% glucose and 40 milliequivalents of potassium chloride per litre of 0·9% saline. Three litres were infused in the first twenty-four hours. On the second day the patient was free of muscular twitching, mentally clear and able to sit and walk without difficulty. His blood pressure had increased to 130 millimetres of mercury, systolic, and 90 millimetres, diastolic; his pulse rate was 75 per minute and his respiration was normal. The plasma electrolyte levels in milliequivalents per litre were as follows: sodium, 142; potassium, 4·2; lithium, 1·8. At this stage he was taking fluids by mouth, and also potassium chloride, one gramme three times a day. He was discharged from hospital the following day.

CASE II.—L.S., a female patient, aged sixty-five years, had been treated with lithium citrate, 21 milliequivalents three times a day, for persistent gross maniacal excitement. When she failed to improve on this treatment, chlorpromazine hydrochloride, 75 milligrammes twice a day, had been given in addition by intramuscular injection. On the fourth day she became drowsy, and a few hours later she was comatose and was transferred to hospital.

She was incontinent of urine and fæces when first examined in hospital, and showed muscular twitches of the forearms and legs, with fasciculation of the small muscles of the hands and face. She was grossly dehydrated with poor peripheral circulation. Her blood pressure was 90 millimetres of mercury, systolic, and 60 millimetres, diastolic, and her pulse rate was 80 per minute. The rectal temperature was 99·3° F. The plasma electrolyte concentrations in milliequivalents per litre were as follows: sodium, 158; potassium, 4·0; lithium, 2·9.

Treatment was started with an intravenous infusion of one litre of glucose (7·5%) in distilled water, to which was added 40 units of soluble insulin and 10 milliequivalents of potassium chloride. This infusion was given in four hours, and was followed by one litre of glucose (15%) and 80 milliequivalents of potassium chloride in distilled water in eight hours. The following morning the coma was much lighter, and at 11 a.m. the patient regained consciousness. The plasma electrolyte levels in milliequivalents per litre were then as follows: sodium, 142; potassium 4·8; lithium, 2·3. Intravenous treatment was continued for the next twenty-four hours with one litre of glucose (5%) in water, and one litre of glucose (5%) in physiological saline, each containing 40 milliequivalents of potassium chloride. The patient was then free of toxic symptoms and was discharged from hospital.

CASE III.—G.L., a female patient, aged seventy-three years, had been treated with 14 milliequivalents of lithium citrate three times a day for about six months, for her agitated senile confusion. She had responded well, and apparently felt well until a few days before her admission to hospital, when she became progressively more confused and finally lapsed into coma.

On examination of the patient in hospital, she showed no response to painful stimuli; the knee and plantar responses were weak, and she had a sluggishly reacting pupillary light reflex. Her extremities were cold and cyanotic, and her skin was dry and wrinkled. She showed twitching of the small muscles of the hands and face and occasional gross limb jerks. She was incontinent of urine and fæces. Her blood pressure was 105 millimetres of mercury, systolic, and 70 millimetres, diastolic, and her pulse rate was 64 per minute, the pulse being feeble but regular. The rectal temperature was 99·4° F. Her respiration was of the Cheyne-Stokes type. She was *in extremis*. The plasma electrolyte concentrations in milliequivalents per litre were as follows: sodium, 155; potassium, 3·8; lithium, 3·5.

Treatment was started with an intravenous infusion of one litre of Darrow's solution in four hours, followed by one litre of glucose solution (5%), to which were added 20 units of insulin, in the next four hours. Her plasma electrolyte levels in milliequivalents per litre were then as follows: sodium, 156; potassium, 5·2; lithium, 2·2. The blood sugar content was 180 milligrammes per 100 millilitres, and there were traces of sugar in the urine. During the next twelve hours two litres of Darrow's solution and one litre of 5% glucose solution were given by the same route. At that stage the plasma electrolyte levels in milliequivalents per litre were as follows: sodium, 154; potassium, 3·8; lithium, 1·7. During the following two days she received intravenously a total of eight litres of fluid—three of Darrow's solution, three of 0·9% saline and two of 5% glucose solution. By this time her coma was much lighter, the plasma electrolyte levels in milliequivalents per litre being as follows: sodium, 160; potassium, 4·1; lithium, 0·8. Oral feeding with fresh fruit juice and light meals together with one gramme of potassium chloride three times a day was possible on the fourth day. On the fifth day she was fully conscious, her peripheral circulation was good, and her blood pressure was 150 millimetres of mercury, systolic, and 90 millimetres, diastolic. The plasma lithium level had fallen to 0·4 milliequivalent per litre, and all evidence of lithium poisoning had passed.

CASE IV.—L.M., a female patient, aged forty-five years, was admitted to hospital in a state of gross confusion. No relevant history was available except that she had been treated with 21 milliequivalents of lithium citrate three times a day for maniacal excite-

ment. When first examined she was ataxic and had muscular twitchings of her hands and face. Her respiration was laboured and irregular. The extremities were cold and mildly cyanotic. Her blood pressure was 100 millimetres of mercury, systolic, and 60 millimetres, diastolic, and the pulse rate was 120 per minute. The plasma electrolyte concentrations in milliequivalents per litre were as follows: sodium, 142; potassium, 3·8; lithium, 4·2.

Treatment was started with an intravenous infusion of glucose (10%) in 0·9% saline, to which was added 60 milliequivalents of potassium chloride per litre. Three litres of this solution were given during the next twenty-four hours, when the patient had become mentally clearer and was able to swallow fluids. The intravenous infusion was stopped, and oral feeding was supplemented with one gramme of potassium chloride three times a day. The patient's clinical condition rapidly improved, and on the second day her blood pressure was 140 millimetres of mercury, systolic, and 90 millimetres, diastolic. On the third day her plasma lithium concentration was 1·8 milliequivalents per litre. On the fifth day she was discharged from hospital.

It is noteworthy that despite the high lithium plasma level this patient, although grossly confused, was never unconscious.

CASE V.—B.W., a male patient, aged thirty-seven years, had responded well to lithium treatment. Prior to this he had been a noisy and aggressive chronic schizophrenic, who had had a prefrontal leucotomy performed without benefit seven years previously. The accurate lithium dosage could not be established, and the medication had possibly been irregular. On his admission to hospital he was grossly confused and ataxic. He had apparently not eaten for several days, and had lost about 30 pounds in weight.

On examination of the patient in hospital, he was found to be cachectic, with loose, dry skin and cold extremities. His respirations were regular at a rate of 20 per minute. His pulse rate was 75 per minute, and his blood pressure was 100 millimetres of mercury, systolic, and 70 millimetres, diastolic. His rectal temperature was 99·5° F. He had excessive thirst and polyuria, but he was continent of urine and fæces. Fibrillation of the small muscles of the hands and face was present, but there were no gross jerks. His plasma electrolyte concentrations in milliequivalents per litre were as follows: sodium, 148; potassium, 4·0; lithium, 4·2.

Treatment was started with potassium chloride, one gramme being given orally three times a day, and an intravenous infusion of one litre of 5% glucose solution, followed by one litre of Darrow's solution and one litre of 0·9% saline in twelve hours. By that time the plasma electrolyte levels in milliequivalents per litre were as follows: sodium, 160; potassium, 3·9; lithium, 3·8. The intravenous infusion was continued during the next twelve hours, the foregoing sequence being repeated. During the first twenty-four hours the patient passed 6·7 litres of urine with a specific gravity of 1·002. During the three days following his admission to hospital he received a total of 13 litres of fluid intravenously—alternating litres of 5% glucose solution, Darrow's solution and 0·9% saline. At this stage the plasma electrolyte levels in milliequivalents per litre were as follows: sodium, 155; potassium, 4·2; lithium, 1·9. By the fourth day the diuresis began to abate and intravenous infusion was replaced by fluids given by mouth, mainly fresh orange juice and egg flips. The oral potassium chloride medication was continued. On the seventh day the plasma electrolyte levels in milliequivalents per litre were as follows: sodium, 155; potassium, 3·9; lithium, 0·2. The blood pressure was 155 millimetres of mercury, systolic, and 90 millimetres, diastolic, and the patient was free from toxic symptoms. He was discharged from hospital.

CASE VI.—C.S., a female patient, aged sixty-five years, suffering from recurrent mania, had been treated with 14 milliequivalents of lithium citrate three times a day for many months, with good control of her maniacal symptoms. During a period of hot weather she began to vomit and became ataxic, and she was sent to hospital.

On examination, she had fasciculation of the small muscles of the hands and face. Her respiration was regular and her blood pressure was 118 millimetres of mercury, systolic, and 80 millimetres, diastolic. Her pulse rate was 70 per minute and regular, and her peripheral circulation was good. She was confused, but not in coma. She had mild diuresis, but was not dehydrated. The plasma electrolyte concentrations in milliequivalents per litre were as follows: sodium, 147; potassium, 4·0; lithium, 2·3. Her blood sugar level was 160 milligrammes per 100 millilitres.

She was able to take fluids by mouth, chiefly fruit juices with glucose, and intravenous therapy was considered unnecessary. She was given 10 units of soluble insulin per day, and one gramme of potassium chloride three times a day. She was free of all toxic symptoms on the third day, and was discharged from hospital on the fourth day.

DISCUSSION

Not all cases of lithium intoxication need be regarded as clinical emergencies. During the period when the six patients presented were treated, some 300 psychotic patients were maintained on lithium therapy, and a number of minor degrees of poisoning were encountered and treated by mere withdrawal of the lithium for several days. Sometimes this was combined with oral administration of potassium chloride, one gramme three times a day. This treatment of minor intoxication is illustrated in Case VI.

The other five case histories presented all illustrate the application of the principles of treatment for more severe grades of lithium intoxication. Although it is difficult to make comparisons of grades of severity, an assessment of the total clinical state is probably a more valid index than the plasma lithium concentration alone. On this basis Cases II and III, in both of which recovery occurred, would seem to be of comparable severity to Cases I and II of Corcoran *et alii* (1949) and to Case I of Hanlon *et alii* (1949), all of which were fatal. The elution of lithium from the body is rapid when potassium is made available for cellular uptake. This is well exemplified in Case III, in which the plasma lithium concentration was initially 3·5 milliequivalents per litre and the

patient was *in extremis*. In eight hours this had fallen to 2·2 milliequivalents per litre, and it was 1·7 milliequivalents per litre twenty hours after the commencement of treatment, with a concomitant improvement in the patient's clinical condition. In three days she had clinically recovered, and the plasma lithium concentration was 0·8 milliequivalent per litre. Case V presents a similar picture, with a plasma lithium fall from 4·2 to 1·9 milliequivalents per litre in three days and to 0·2 milliequivalents per litre on the seventh day.

Intracellular lithium would seem to exert its effect *in vivo* by interfering with essential intracellular potassium-dependent metabolism. Infused potassium in cases of lithium intoxication largely disappears from the circulating plasma in a short time, indicating a fairly rapid cellular uptake. In Case II, for instance, the infusion of 90 milliequivalents of potassium in a twelve-hour period resulted in a plasma potassium concentration rise of only 0·8 milliequivalent per litre and a rapid elution of lithium from the body. In all cases the final serum potassium concentration indicated that most of the infused potassium must have passed into intracellular fluid. Furthermore, it appeared that lithium excretion following potassium infusion was considerably greater than would have occurred on mere withdrawal of lithium medication. In no case was the serum sodium concentration low before the institution of therapy, and massive sodium infusion would seem to have no place in the specific therapy of lithium intoxication. Sodium may be required to counteract metabolic ketosis or to expand extracellular volume; but there is no evidence that gross sodium depletion is a feature of this syndrome.

Lithium is a valuable form of treatment in conditions of psychomotor over-activity, and is a specific therapeutic agent in manic psychosis. With adequate clinical and biochemical control, its use should rarely give rise to states of severe intoxication; but should this emergency occur, treatment along the lines indicated can be expected to produce a satisfactory reversal of the toxic state.

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MUCOID IMPACTION OF THE BRONCHI[1]

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SUMMARY

Seven cases illustrating the syndrome of mucoid impaction of bronchi are described.

The syndrome seems to be confined to asthmatics. It may be clinically silent for long periods, or it may lead to bronchiectasis, pulmonary infection and hæmoptysis. Radiologically it may show both peripheral and hilar components. Diagnostically it may be confused with pulmonary tuberculosis, neoplasm or Loeffler's syndrome.

Treatment is primarily medical. Adrenal corticoids may aggravate infection and are contraindicated. Surgical resection may be necessary to remove areas of destroyed lung or when a differentiation from bronchial carcinoma is impossible on clinical grounds.

Lobectomy was performed in two cases only in this series, and the examination of operation specimens showed bronchi occluded by eosinophilic mucous material. There was inflammation with disorganization of the bronchial walls, and the alveoli showed collapse and lipoid pneumonia.

It is considered that the syndrome described represents a more benign and localized variant of the widespread mucus obstruction of small bronchi found in fatal cases of *status asthmaticus*, and that both have their basis in a quantitative or qualitative disorder of bronchial mucus secretion in asthmatics. This disorder may be present even when clinical asthma is temporarily absent.

IT is well known that in patients dying in *status asthmaticus* the smaller bronchi and bronchioles are frequently found to be partially or completely occluded by mucous secretion. Chronic asthmatics and some sufferers from chronic bronchitis also cough up thick, tenacious mucoid material.

Robert Shaw in 1951 drew attention to a distinct clinical entity, occurring in patients suffering from bronchial asthma or "chronic obstructive bronchitis", which he termed mucoid impaction of the bronchi. This syndrome results from the local accumulation of inspissated mucus, particularly in the segmental bronchi just distal to a bifurcation. This local accumulation grows in size layer by layer and eventually dilates the bronchus in which it is impacted. Unless such plugs are coughed up, a number of sequelæ may result—segmental atelectasis, pulmonary suppuration, bronchiectasis, and pressure obstruction of adjoining bronchi. These features may produce clinical and radiological pictures which are easily confused with those of pulmonary tuberculosis and bronchial carcinoma.

It is paradoxical that, at a time when radiology is adding much to our knowledge of intrathoracic disease, Shaw's contribution should have been based on a series of erroneous radiological diagnoses. In fact, in five of his ten cases the patients were submitted to surgical resection on the basis of a radiological diagnosis of probable bronchial carcinoma. The pathological specimens thus provided led to an awareness of the condition of mucoid impaction of bronchi.

A similar pattern has evolved in our own clinic. In two cases resection of part of the lung was carried out because of diagnostic confusion before we were aware of Shaw's description. Study of the resected specimens and knowledge gained from the visit to Sydney of Dr. Shaw in 1954 have enabled us to make a confident diagnosis of the syndrome in three other cases of asthma.

It is our purpose to add these five cases to the sparse literature on this curious syndrome, as we believe it merits wider recognition than has hitherto been given it. It will become apparent that there is a pattern to these cases which should enable the physician to distinguish them from tuberculosis and neoplasm. Furthermore we suggest that many cases described in the literature as Loeffler's syndrome in asthmatics may well have been examples of mucoid impaction.

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[4] Aided by a grant from the National Health and Medical Research Council.

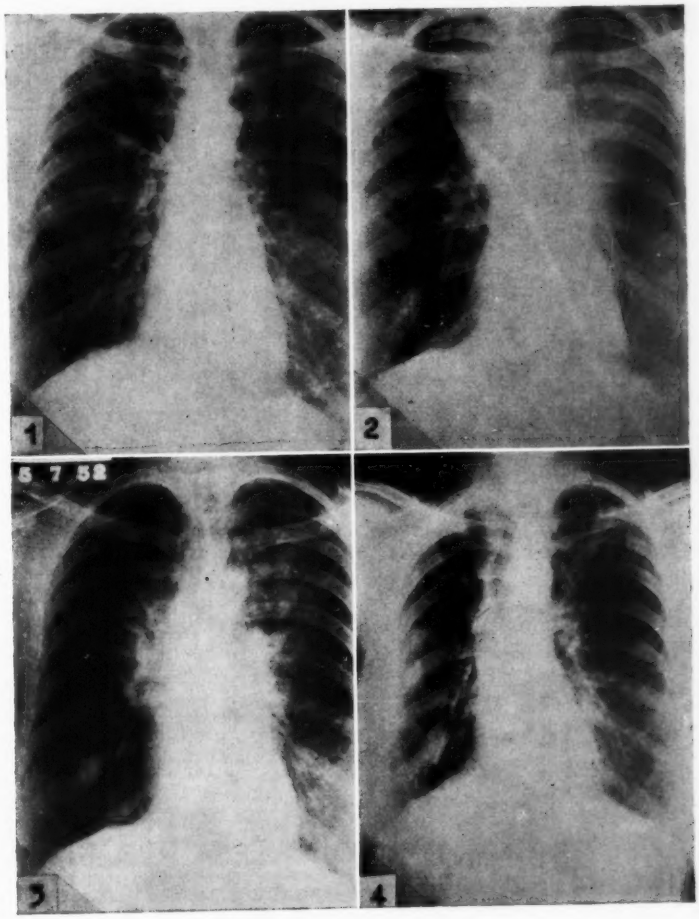
REPORTS OF CASES

CASE I.—Mrs. E.M., aged fifty-seven years, was admitted to the Royal Prince Alfred Hospital in August, 1951, for investigation following an X-ray examination of her chest. She gave a history of recurrent attacks of asthma and bronchitis for many years, but her health generally had been good. She had family contact with two cases of pulmonary tuberculosis.

A skiagram of her chest (Figure I) revealed linear infiltrations in the upper lobe of the right lung and the subapical region of the left lung. The result of the Mantoux test was positive, but her sputum on repeated examination failed to show tubercle bacilli. Her leucocytes numbered 6600 per cubic millimetre, of which 3% were eosinophile cells.

It was decided that she should remain under observation as a patient with pulmonary tuberculosis of doubtful activity. Her basic symptoms remained, of cough, intermittent dyspnœa and wheeze; and occasionally râles were heard over the front of the left side of her chest.

In March, 1952, her chest X-ray film showed dullness on both sides of the mediastinum (Figure II), and by



FIGURES I TO IV

Serial X-ray films from the patient in Case I taken at the time of admission to hospital and seven and eleven months and four years later. Linear infiltrations in the upper lobe of the right lung and subapical region of the left lung developed into diffuse opacities in both upper lung fields, suggesting an enlarging mediastinal tumour. After twenty-one months the right upper lobe was removed at operation, and shortly afterwards, after the coughing up of numerous small hard pellets, the left upper lobe cleared

July she was reported to have "a diffuse, poorly defined opacity in the upper half of the right chest and apparently extensive infiltration in the left upper lobe" (Figure III). The appearance was now suggestive of an enlarging mediastinal neoplasm, and thoracotomy was considered but rejected by the patient.

Increasing symptoms and signs finally led to her readmission to hospital in May, 1953. The chest X-ray appearance had not changed in the past ten months. It was decided that her chest should be explored with the object of relieving pressure, as distressing dyspnœic attacks were now becoming frequent. To the general surprise thoracotomy by Mr. J. S. McMahon revealed a discrete and freely movable mass in the upper part of the chest on the right side, which on dissection proved to be the upper lobe of the right lung. It was removed without difficulty. The pathologist, Dr. V. J. McGovern, reported on this as follows:

> The specimen consists of the upper lobe of the right lung. Throughout there are large tubular nodules which are found to be composed of inspissated secretion lying within grossly dilated and cystic bronchi. This secretion is partly mucoid and most of it is very dense and of the consistency of cartilage. There are small areas of consolidation due to pneumonia at the periphery of the lung (Figure XIX).

Dr. McGovern was unable to determine the pathological nature of the lesion, confessing that he had never seen anything like it before.

Meanwhile during a stormy post-operative period the patient coughed up numerous small hard, round pellets, the size of marbles. At the same time the opacity in the upper lobe of the left lung underwent a surprising clearing, until only streaky residual infiltration remained, together with a few doubtful cystic spaces. The patient left hospital reasonably well though still short of breath. Her chest X-ray films have shown no significant alteration up to March, 1956 (Figure IV).

When last seen, in April, 1956, she was not very well, being more breathless and complaining of increased cough and sputum, sometimes lumpy. Her physical signs were characteristic of asthma.

This asthmatic patient was referred originally because of symptomless radiological infiltration of the upper lobes of both lungs. She was first thought to have pulmonary tuberculosis, but tubercle bacilli were never found despite extension of the radiological abnormalities over a two-year period. Deferred for a time by a high eosinophilia (1500 per cubic millimetre) and the possibility of allergic pneumonitis, thoracotomy finally revealed a cystic functionless upper lobe of the right lung. This specimen remained a medical curiosity until its nature was confirmed by Dr. Robert Shaw when he visited Sydney. The presence of asthma, the long clinical course and the nature of the sputum were characteristic of the condition which Shaw described, and served (in retrospect) to distinguish the disease from neoplasm. Further confirmation was obtained when the left apical lesion cleared after the patient coughed up hard, round pellets.

CASE II.—L.B. was forty-one years old when he first came under our care in June, 1953. He had suffered from asthma and "recurrent bronchitis" for the previous thirty-eight years. He had had no known contact with tuberculosis.

In March, 1953, he had developed increased cough, producing about two ounces of yellowish sputum each day. This sputum was sometimes stringy, and hard to cough up. In May, 1953, his sputum had been stained with blood for several days, and a chest X-ray film taken subsequent to this had shown patchy consolidation throughout the upper lobe of the right lung (Figure V). He had recently gained over a stone in weight. He looked well, and physical examination revealed no abnormality. The findings of a blood count were within normal limits with a normal erythrocyte sedimentation rate. The Mantoux reaction was positive. Five specimens of sputum were examined for tubercle bacilli with negative results. A provisional diagnosis of pulmonary tuberculosis was made, treatment was begun with streptomycin and para-amino-salicylic acid, and he was sent to a sanatorium. The chemotherapy was continued for three months, by which time his chest X-ray film had shown very considerable clearing of the opacities in the upper lobe of the right lung (Figure VI).

In March, 1954, he again had a small hæmoptysis, and chest X-ray examination showed regression of the lesion in the right upper lobe. In April, 1954, a further X-ray examination (Figure VII) showed partial atelectasis of the right upper lobe. Bronchoscopic examination revealed a narrowing of the orifice of the bronchus to the posterior segment of the right upper lobe. This stenosis was thought to be tuberculous in origin, and treatment was again instituted with streptomycin and para-amino-salicylic acid. But by June, 1954, the radiological appearances had deteriorated still further (Figure VIII), and he had had some further small hæmoptyses. Dr. A. McIntosh, of Queen Victoria Sanatorium, wrote as follows: "His sputum is of an unusual character—tough, homogeneous and containing few cells."

In July, 1954, he was readmitted to Royal Prince Alfred Hospital. Chest X-ray examination still showed a partial collapse of the right upper lobe, though in the interim the consolidation had waxed and waned considerably. It was felt that only surgical exploration of the chest could elucidate the diagnosis, and on August 5, 1954, Mr. J. S. McMahon performed a right upper lobectomy and a four and a half rib thoracoplasty. Post-operative convalescence was uneventful.

Examination of the resected specimen showed the typical appearances of mucoid impaction of the bronchus. There was stenosis of the posterior branch of the right upper lobe bronchus, and distal to this the bronchus was ballooned to a diameter of two centimetres by a mass of greenish-grey material, which was quite firm and appeared brown and translucent at the margin. Some of the bronchi distal to the impaction contained creamy gelatinous material.

This patient continues to have frequent attacks of asthma and of bronchitis. He has occasional hæmoptyses, and coughs up rubbery "plugs" of sputum from time to time. During 1955 his chest

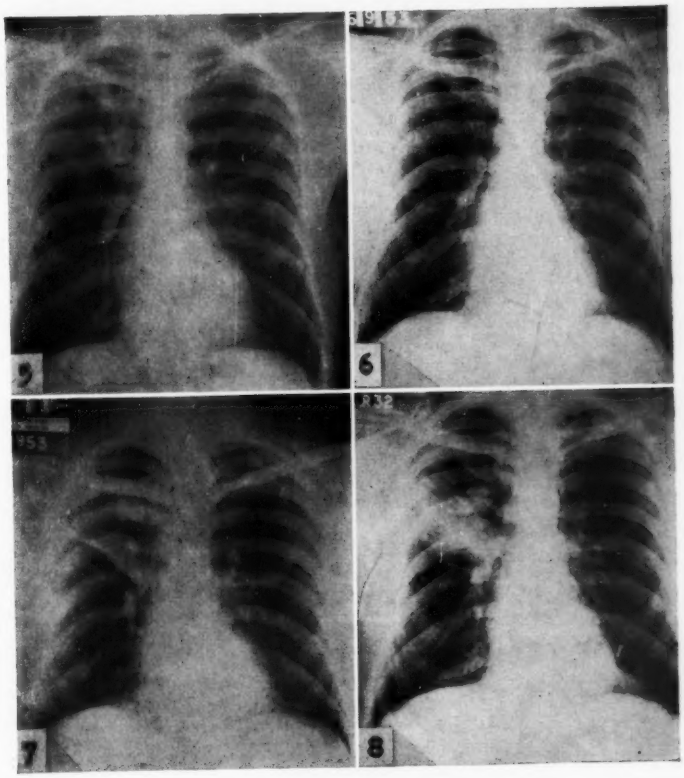
X-ray film at one time showed a good deal of opacity in the left lower lobe, but this has subsequently cleared completely. A bronchogram performed early in 1956 showed no gross bronchial abnormality.

This patient's illness began with hæmoptysis and right upper lobe infiltration. Although his sputum did not contain tubercle bacilli, he was treated for tuberculosis, and the favourable response to chemotherapy seemed to confirm the diagnosis. Subsequent regression when treatment was stopped and the finding of bronchostenosis appeared to support this, but further chemotherapy did not prevent deterioration. This deterioration, the unusual character of the sputum and the instability of the radiographs led to thoracotomy and resection. Subsequent follow-up for two years has shown no permanent deterioration due to segmental disease elsewhere, but the patient still has asthma. There are slight bronchographic abnormalities in the lingula.

Histopathology in Cases I and II

On histopathological examination it was found that the bronchi were filled with an eosinophilic mucous material which almost completely occluded them. The mucus contained strands of cells, macrophages, lymphocytes and eosinophile cells. This material could be seen in both small and large bronchi.

In some areas the bronchial epithelium was lost. In areas where it remained, there were very numerous goblet cells, in some places multilayered and contiguous for some distance. There were redundant folds of bronchial mucosa and, between some of these, mucosal herniations

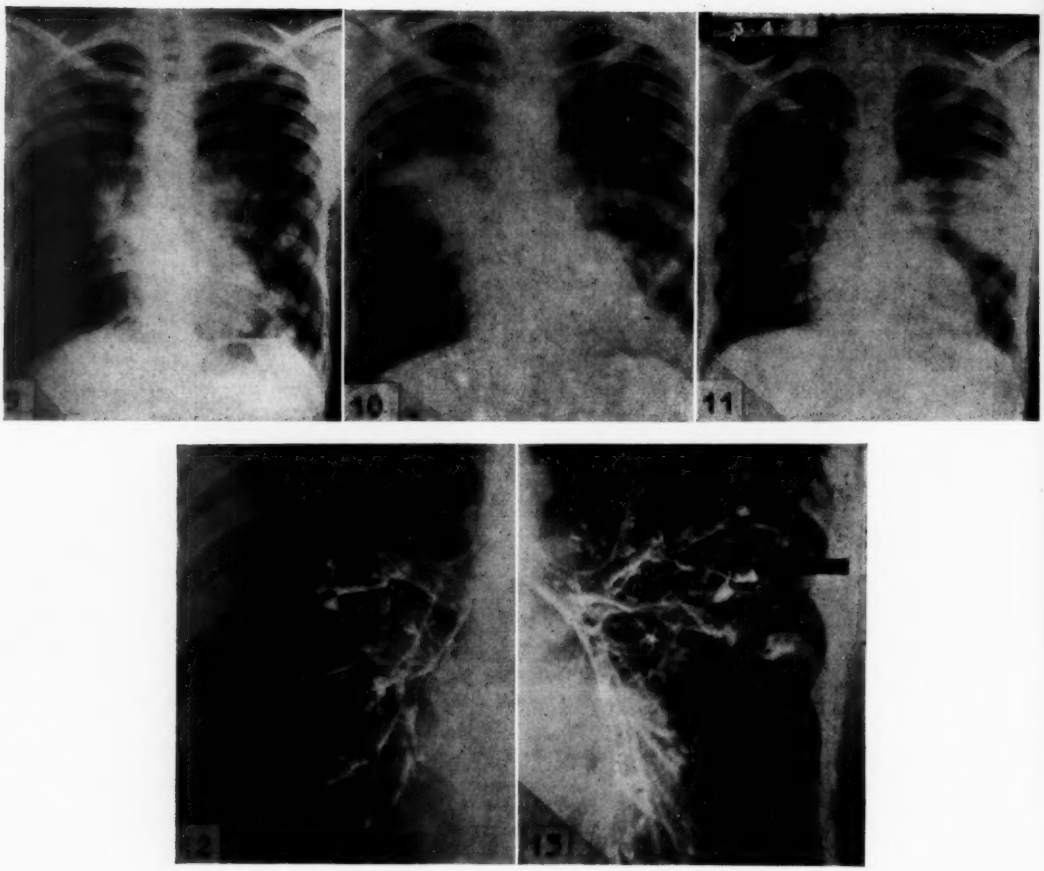


FIGURES V TO VIII

X-ray films from the patient in Case II showing variations in the opacities in the upper lobe of the right lung over a year. Lobectomy was performed one month after the last film was taken and revealed typical mucoid impaction of the bronchi

down through the *muscularis mucosæ*. The walls of the bronchi were infiltrated with numerous cells, chiefly lymphocytes, and in some areas the normal structure of the wall was completely destroyed.

In many areas there were gross changes in the alveoli in relation to affected bronchi. These were mainly of the nature of collapse and chronic lipoid pneumonia such as one sees in association with chronic bronchial obstruction or bronchiectasis.



FIGURES IX TO XIII

Varying opacities in both lung fields (Case III). The first film shown (Figure IX) was taken in July, 1955. The subsequent films were taken four and nine months later. At thirteen months the X-ray appearance was normal, but bronchograms (Figures XII and XIII) showed bilateral bronchiectasis

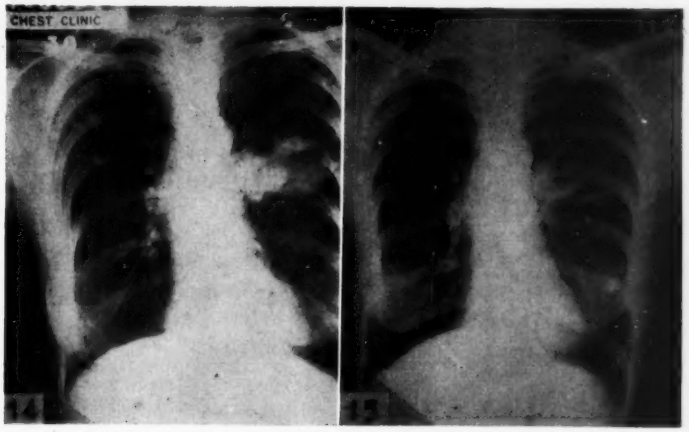
CASE III.—C.N., aged fourteen years, was referred to the Thoracic Unit from the Asthma Clinic because of a possible tuberculous lesion in the upper lobe of the right lung. He had been asthmatic since childhood. A miniature chest X-ray film in 1954 had shown no abnormality. When first seen by us on April 7, 1955, he had no asthma and had been free of it for some months. He was a tall lean lad with no abnormalities on physical examination. His weight was seven stone, eight pounds. The Mantoux reaction was negative with 1 : 1000 and subsequently 1 : 100 old tuberculin. Sputum and gastric washings contained no tubercle bacilli on culture. The hæmoglobin measured 17·3 grammes *per centum*, and the white cells amounted to 6600 per cubic millimetre, with eosinophile cells 1% of the total. The erythrocyte sedimentation rate was eight millimetres in one hour (the upper limit of normal by the Hawksley method). A lordotic view of the chest confirmed the presence of increased mottling in the upper zone of the right lung. No treatment was given.

No clinical or radiological change occurred until July, 1955, when mottled opacities were seen in the

right upper and left lower lobes. At this time there were no physical signs, the boy felt well and he had gained six pounds in weight. Two weeks later further extension of the lesions in the right upper and left lower lobes was seen (Figure IX). He had lost one and a half pounds in weight, but he felt well and was afebrile. He coughed only occasionally and produced a little "white, thick phlegm". There were no abnormal physical signs in the chest. His white cell count was 16,750 per cubic millimetre, neutrophile cells being 53%, lymphocytes 26%, monocytes 4%, eosinophile cells 16% and basophile cells 1% of the total. The erythrocyte sedimentation rate was 10 millimetres in one hour. No treatment was given. On August 8, 1955, no definite radiological or clinical change was found. On August 23, much clearing had taken place in the upper zone of the right lung. A few rhonchi were heard over the lower lobe of the left lung, and no significant change in weight had occurred.

On December 23 his chest was normal clinically. Radiologically there was considerable resolution of the right upper lobe lesion. A small cavity was seen where the mucus plug had been impacted in the right upper lobe bronchus, and the boy stated that he had coughed up some plugs of mucus. He remained well until March, 1956, when he reported with fever, anorexia and pleural pain in the left axilla. There was no cough or sputum. Examination showed dullness and a friction rub in the involved area, and a skiagram showed a triangular shadow at this site (Figure XI).

He responded quickly to oxytetracycline, but the triangular shadow was unchanged three weeks later. After a second bout of fever and antibiotic therapy he coughed up some thick yellowish sputum over forty-eight hours and had no further trouble. The



FIGURES XIV AND XV

X-ray films of the patient in Case IV showing spontaneous clearing of opacities in the mid-zone of the left lung. The interval was seven months

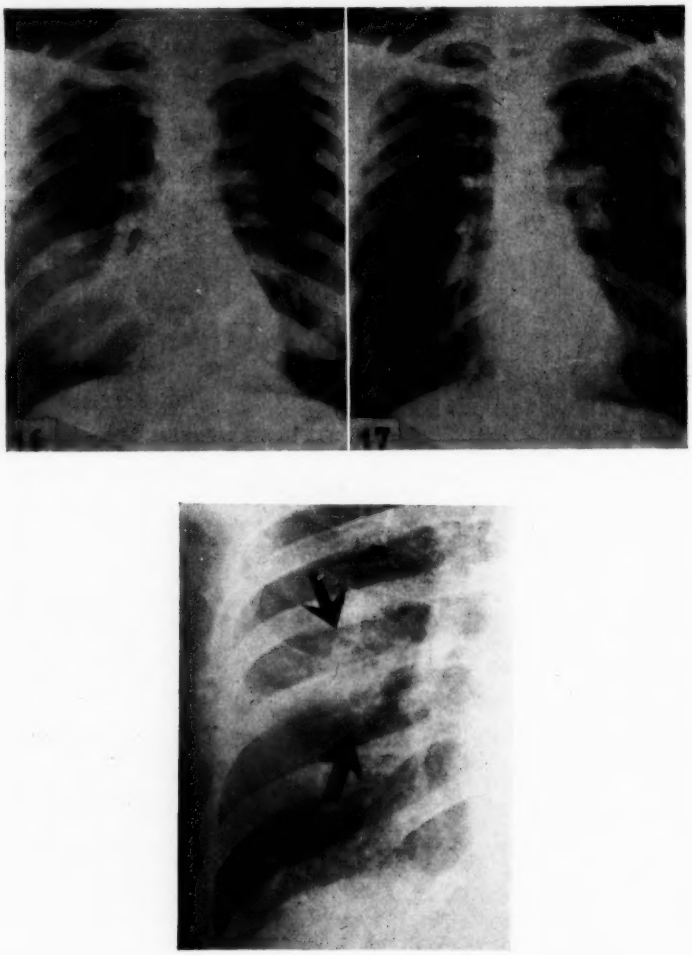
Throughout September and October no change in the radiological picture was seen; the boy gained six pounds in weight and played tennis every Saturday. The leucocyte count returned to normal. On October 11 his chest film showed persisting opacities in the left lower lobe with a residual opacity near the right hilum.

At this stage it was decided to try the effect of cortisone. One hundred milligrammes daily were given for a week, and the dosage was then reduced to 50 milligrammes daily. After ten days he became ill with anorexia, sweating, fever and tachycardia. He was admitted to hospital on November 9. His temperature was 104° F., his pulse rate 120 per minute, and his respiratory rate 23 per minute. There was dullness to percussion in the right axilla with a friction rub and occasional crepitations. The leucocyte count was 19,400 per cubic millimetre with 93% neutrophile cells. The chest X-ray film showed consolidation of the anterior segment of the right upper lobe (Figure X). He responded partially to penicillin and was discharged from hospital on November 13 in order to take a school examination. He took chlortetracycline while at home and gradually

radiological shadow in this episode persisted for at least one month. When seen next in August, 1956, he had gained eight pounds in weight and felt very fit. He had had no asthma and remarked that he now realized that he had been "off colour" over the preceding twelve months. Radiologically his chest was clear, but a bronchogram revealed saccular dilatation of the anterior division of the right upper lobe bronchus near its origin (Figure XII); less marked saccular bronchiectasis of the same segment on the left side and the upper division of the lingula bronchus (Figure XIII); and cylindrical bronchiectasis of the anterior and lateral basal bronchi of the left lower lobe. The situation and shape of the saccule in the right upper lobe corresponded exactly with that of the mucus plug seen previously on the radiographs (Figure IX).

This boy's case was unique, in that we were able to follow his illness from its onset with minimal radiological abnormalities in the right apex through a bewildering sequence of infiltrations, atelectases and consolidations to complete

recovery. The bronchographic demonstration of bronchiectasis and its close correlation with the areas of "infiltration" leave little doubt of the nature of the illness. A number of points need emphasis. The first is the long history of asthma and its complete absence during the whole course of the present illness. No rhonchi were heard during 25 recorded examinations of the chest. The second is the peripheral location of the earliest radiological abnormality with the appearance only after some months of the tell-tale mucus plug and segmental atelectasis. The third is the comparative well-being of the patient punctuated on three occasions, each of only a few days, by an acute febrile reaction which responded to antibiotics. The fourth is the absence of cough, sputum and physical signs despite extensive radiological abnormalities. The fifth is the rapid disappearance of these abnormalities



FIGURES XVI TO XVIII

X-ray films of the patient in Case V. The shadow in the lower lobe of the right lung (Figure XVI) had cleared one month later. After a further twelve months opacities appeared in the left mid-zone (Figure XVII), and these also disappeared in four months. Figure XVIII is a representative film of those taken in the two years preceding Figure XVI and shows an infiltrate in the same part of the lung

when the obstructive plugs were coughed up. The sixth is the occurrence at one stage of eosinophilia and our misdirected therapy with cortisone, which showed quite clearly that the illness was not of an allergic nature.

CASE IV.—Mrs. M.R., aged fifty-nine years, was seen in July, 1954, after an attack of left-sided "pleurisy". She had been a sufferer from asthma since the age of four years, but had not had a bad attack for some years.

Her chest X-ray film in July, 1954, revealed lumpy infiltration in the left mid zone near the hilum, with increased radial markings under the right clavicle (Figure XIV).

The physical signs were those of emphysema.

In hospital her Mantoux reaction was positive, and her leucocytes numbered 9950 per cubic millimetre, with eosinophile cells 5% of the total. Her sputum on smear and culture failed to yield tubercle bacilli.

She was treated with bed rest, streptomycin and PAS, and her convalescence was rapid. She soon lost symptoms, and the radiological improvement was surprisingly complete. Antibiotics were given up as the diagnosis of tuberculosis seemed doubtful after three months. By February, 1955, the left mid zone had cleared almost completely, though there was a simulation of cavitation in this region (Figure XV). She still has slight asthma.

In this asthmatic patient fever and pleuritic pain led to the recognition of pulmonary infiltration. This clinical episode resembled those described in Case III, and there was a similar absence of abnormal physical signs. Likewise she had had no recent asthma. Like the patient in Case II, she was thought to have pulmonary tuberculosis and responded to streptomycin. In retrospect the radiological appearances were unusual for tuberculosis, and it is felt that the rounded opacity and the cavity that succeeded it near the hilum represent the site of the mucoid impaction.

CASE V.—Mrs. H.K. was first seen in the Thoracic Unit in March, 1950, when she was forty-nine years of age. She had been treated for asthma for twelve years. Skiagrams of the chest from 1947 to 1949 showed minimal fibrotic changes in the left apex. A routine film taken on March 9, 1950 (Figure XVI) showed an extensive opacity in the right middle lobe, which had largely resolved two weeks later. She had had a morning cough for six months, but her asthma was not troublesome. Her chest moved poorly, but the breath sounds were vesicular, and there were no râles or rhonchi. The white cell count was 6450 per cubic millimetre, with 11% eosinophile cells.

She remained well through 1950, but a film taken on April 10, 1951 (Figure XVII), showed some mottling in the anterior segment of the left upper lobe, with a rounded opacity at the related hilar zone and some slight infiltration in the right lower lobe. One month later there was patchy infiltration of the left lower lobe, but the left upper and right lower lobes had cleared. She had no symptoms, and a film taken four months later showed clearing of the lower lobe opacities. One year later (May 20, 1952) they recurred, but she remained well despite persistence of the radiological lesions, until January, 1954. At that time the leucocytes numbered 8300 with 9% eosinophile cells. Subsequent observation to March, 1956, has shown no return of these opacities; the fibrotic lesions at the left apex persist unchanged. The Mantoux reaction is positive, but tubercle bacilli have not been found in the sputum in eleven examinations.

It is possible that this asthmatic patient had an inactive tuberculous lesion at the left apex. However, it may have been due to old mucoid impaction. She was referred to us because

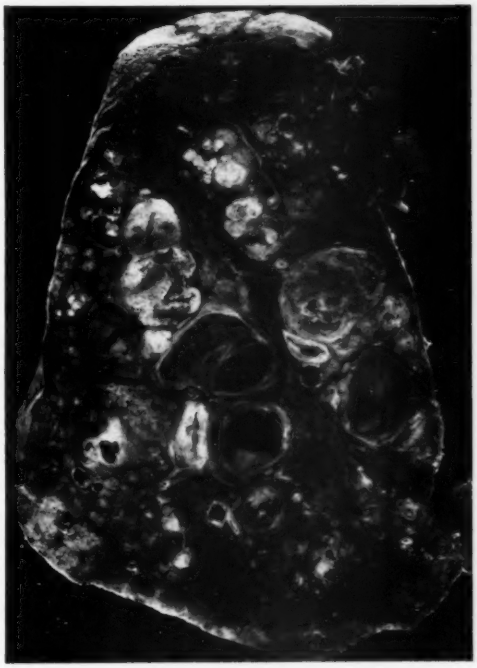


FIGURE XIX

The resected upper lobe of the right lung in Case I after section. Note the large masses of inspissated mucus lying in bronchi of all sizes, and the dilatation of the bronchi from which the plugs have fallen during handling

of the extensive opacity in the right middle lobe, which was thought to be due to a spread of her old tuberculous disease. The absence of symptoms, the presence of eosinophilia and the rapidity of clearing all suggested Loeffler's syndrome, a diagnosis which was again considered when the results of a blood count were abnormal four years later. The "extension" of the lesion to the other parts of the left lung seemed at first to support the diagnosis of pulmonary tuberculosis, but the absence of

symptoms, the persistently negative bacteriological findings and the eventual complete resolution surely rule out that diagnosis. On the other hand, the whole "illness" occurring in an asthmatic subject appears quite compatible with obstruction of the smaller bronchi.

DISCUSSION

Clinical Features

Mucoid impaction appears to be restricted almost entirely to asthmatics. It may begin insidiously at a time when the patient is free from asthma. At the outset it is probably always symptomless and discoverable only by radiography.

Its recognition may be delayed until superadded infection leads to hæmoptysis, pleurisy or patchy pneumonitis. The absence of symptoms usually contrasts with the extent of the radiological findings. This may be so for many months, but in all but one of our cases symptoms ultimately developed. Similarly physical signs are frequently lacking, and even the characteristic rhonchi of asthma may be missing. Only three of our patients are known to have coughed up the mucus plugs, although this must have occurred in those who recovered without operation.

The blood count in general is uninformative. The sedimentation rate is normal when infection is absent. Three of our patients had transient eosinophilia (700, 1500 and 2600 cells per cubic millimetre), which in one was associated with neutrophile leucocytosis. Eosinophilia is a recognized feature of uncomplicated asthma even between attacks (Bray, 1937) and is therefore of no diagnostic assistance. It may even be misleading if it leads to a hasty diagnosis of Loeffler's syndrome.

Pathology

The pathological features of the resected lobes correspond closely with Shaw's description. The bronchi of all sizes show eosinophilic mucus plugging, inflammatory infiltration of the walls, hypertrophy of the mucous glands and herniations of the mucosa through the *muscularis mucosæ*. The surrounding lung shows inflammation. The morbid anatomy of the smaller peripheral lesions has not been described. Nevertheless, it is likely that these too are due to obstruction of the smaller bronchi with collapse-consolidation. Such changes have been reported by Gloor (1954) and earlier writers in asthmatic subjects dying from *status asthmaticus* or intercurrent disease. In view of the finding of Mears *et alii* (1953) that bronchial stenosis occurs frequently in asthmatics, it is of interest that in Case II the patient had severe stenosis of the bronchus to the posterior segment of the right upper lobe. Shaw found no stenosis in his cases.

Hypertrophy of the mucous glands is characteristic of asthma, and secretion appears to be excessive even when asthmatic paroxysms and rhonchi are absent. Obstruction should occur in the smaller rather than the larger bronchi. At the outset this was true in all our cases. The larger plugs which obstruct second degree bronchi are built up more slowly and may be almost cartilaginous in consistency. The evidence from Case III shows that they may produce saccular dilatation of the bronchus at the site of impaction within a few months of the onset of the disease. Even when they have persisted for much longer, they may ultimately be coughed up, thus providing a natural cure. If the patient escapes bronchiectasis, the cure may still not be complete, for fibrotic lesions may persist in the affected area. Radiologically, we have found evidence of apical fibrosis in a number of asthmatics since becoming aware of their probable significance.

Radiology

Shaw noted the shadows produced by the mucus plugs themselves and also those due to infection and collapse in the related segments. He also observed radiological clearing of one segment while the process was reappearing in another. At times the sharply circumscribed shadows may disappear without trace.

In the present series the lesion began peripherally in all five cases. In all it began in the upper lobe. In Case III it was first recognized as a soft, hazy opacity in the infraclavicular region, which was succeeded four months later by a more central opacity taken to be an obstructing plug, with early collapse and infiltration of the anterior segment of the right upper lobe (Figure IX). In Case I there was a similar soft infiltrate on the left side of the earliest X-ray film, accompanied by some atelectasis and infiltration of the right upper lobe (Figure I). In Case II both a peripheral infiltrate and a large hilar shadow were seen at the first visit (Figure V). In Case IV there was also a small right apical infiltrate, but the most striking lesion was a very large multilobular opacity at the left hilum (Figure XIV). In Case V the patient was referred after consolidation-collapse of the right middle lobe, but review of the films covering the previous two years showed an earlier infiltrate in the same region (Figure XVIII) and a subsegmental collapse in the right upper lobe.

Large, lumpy, rounded, dense, hilar or parahilar opacities are the second radiological feature, and these were seen in four out of the five cases. Like the peripheral lesions they too may disappear and reappear in other sites. In Cases II, III and IV these opacities were hilar, but in Case I they were scattered throughout both upper lobes.

In Cases I and II removal of the right upper lobe confirmed the identity of the shadows with the mucus plugs, and it was of interest that similar shadows in the left upper lobe disappeared as the patient in Case I coughed up mucus plugs.

Bronchography provides valuable information of obstruction or, when the plugs have been coughed up, of bronchiectasis. In addition it has confirmed the nature of the parahilar opacities. From the two patients who have had bronchograms we have learnt that the bronchiectasis may be strictly localized, or it may involve many segments of the lung in this disease.

Asthma and Loeffler's Syndrome

It was noted that three of our patients had eosinophilia at some time in their illness and could perhaps be regarded as having Loeffler's syndrome. Apley and Grant (1944) write: "Loeffler's description of his radiological findings is embarrassingly comprehensive. He describes shadows 'in any position and of any size, of variable structure, homogeneous or more frequently patchy or cloudy, more or less sharply circumscribed, single or multiple, unilateral or bilateral'." In their paper on pulmonary eosinophilia Crofton and his colleagues (1952) report eight cases of Loeffler's syndrome occurring in asthmatics. In most of their cases the eosinophilia was neither constant nor striking and could have been related as much to the chronic asthmatic state as to the pulmonary infiltration. These authors found that bronchiectasis of some degree was present in seven of their eight cases, and also noted that the bronchiectatic segment could frequently be related to the "infiltrates", which may have been due to atelectasis.

In their excellent bibliography they refer to many earlier descriptions of transient infiltrations in asthmatics, and in many, but not in all, the importance of segmental disease and the inconstancy of eosinophilia is striking (Alpher, 1947; Karan and Singer, 1942).

Some of these cases resemble closely our own cases in which operation has not been performed. In other cases in the literature the "infiltrates" are more fleeting and may last only a few days (Gottdiener, 1945). Their occurrence in asthmatic subjects was recognized long before Loeffler's description of pulmonary eosinophilia appeared. Bezancon *et alii* (1939) remarked that they might be due to atelectasis—massive, lobar (Clarke, 1930), or lobular. They also remarked on, and in their case histories illustrated, the inconstancy of eosinophilia in relation to the lesions. In other cases, however, they felt that asthmatic allergy declared itself at an alveolar rather than a bronchiolar level and that the lesion was thus more truly an infiltrate. Strand (1943), Breton (1938) and Harkavy (1941) have also considered the patches in the lung in asthma to be due to atelectasis.

Unfortunately the few autopsies in asthmatic patients with Loeffler's syndrome have been performed some time after the infiltrate has disappeared. In Strand's second case, however, autopsy did show bronchial distension and obstruction with signs of recent inflammation. Likewise bronchograms have seldom been performed except by the Brompton Hospital group, and at present the presence of bronchial obstruction or dilatation requires further confirmation.

From the literature it is apparent that the eosinophile cell count in uncomplicated asthma is very variable. During the attack it tends to be lower than in the asymptomatic intervals. Bray (1937) quotes eosinophile cell counts from nil to more than 20% of the white cells and notes that the total number of white cells may also exceed 15,000 per cubic millimetre. It is therefore not surprising that, when pulmonary infiltrates occur, the eosinophile cell count also varies. Thus Crofton *et alii* remark that "some patients have eosinophilia in some of their attacks but not in others which are in every other way identical".

Another reason for difficulty in the interpretation of eosinophilia lies in its occasional occurrence in the recovery phase of simple pneumococcal infections of the lung. This appears to be the explanation for some cases reported in the literature as Loeffler's syndrome.

Finally, there is a rare group of diseases involving the lung in which asthma, eosinophilia and pulmonary infiltration may occur alone or be associated with manifestations of vascular allergy and granulomatosis in other parts of the body (Harkavy, 1941; Ehrlich and Romanoff, 1951; Fienberg, 1955). The presenting symptom may be hæmoptysis or apparent pulmonary infection. The X-ray appearances are extremely varied, ranging from peribronchial infiltration to multiple fluffy opacities, solitary nodules or areas of

atelectasis. The clinical features are, on the whole, more dramatic than in mucoid impaction; there is a hectic course, and many cases terminate fatally. They closely resemble *polyarteritis nodosa*, one of the accepted causes of Loeffler's syndrome.

Despite the occurrence of these unusual examples of what is at present regarded as true pulmonary allergy, it is considered that, in asthmatic subjects at least, the majority of infiltrates are usually obstructive or infective in origin. The diagnosis of Loeffler's syndrome should be made only when it is certain there is no primary bronchial pathological condition. Therapeutically, the distinction is important, for adrenal steroids may be lifesaving in true allergic states, but in mucoid impaction they are not helpful and may encourage infection and destruction of lung tissue.

Differential Diagnosis

Pulmonary Tuberculosis. — When mucoid impaction begins peripherally, the radiological appearance may resemble closely that of a tuberculous infiltrate. At a later stage hæmoptysis and a partially contracted upper lobe may add to the resemblance. The radiological behaviour of the infiltrate when antibiotics are given may also be compatible with this diagnosis. At other times its too rapid clearing or its reappearance in other zones may give the clue to the diagnosis of mucoid impaction. Shadow for shadow, the individual lesions may be indistinguishable, but the asthmatic history, the character of sputum, the absence of tubercle bacilli and less surely the comparative well-being of the patient would help in ruling out tuberculosis.

Neoplasm.—The occurrence of a pulmonary infection, frequently with hæmoptysis, and with a large atelectatic element seen radiologically, must lead to a suspicion of bronchial carcinoma in many cases. Bronchoscopy, bronchography and sputum cytology may be of assistance in differential diagnosis, but occasionally thoracotomy with removal of the affected lobe will be indicated to clarify the issue. Our patient in Case I was submitted to surgical operation on this basis.

Loeffler's Syndrome and Vascular Allergy.— The distinction from Loeffler's syndrome and vascular allergy has been discussed sufficiently above.

Treatment

In the absence of precise knowledge concerning the abnormal mucoid secretions in asthmatics, treatment must be largely directed to meeting complications as they arise. Vigorous physiotherapy may aid the displacement of mucus plugs, as is borne out by the satisfactory results obtained on the left side in Case I in the post-operative period. Once the obstructing plug is dislodged, infective sequelæ, short of bronchiectasis, in the related lung segment will be brought quickly under control. Bronchoscopic removal of the plugs is impracticable by virtue of their position in the segmental bronchi.

Appropriate antibiotic therapy will be indicated during infective episodes, but should be combined with physiotherapy to allow adequate bronchial drainage.

As pointed out earlier, ACTH or cortisone may do considerable harm by encouraging infection and tissue destruction. This was certainly so in Case III of our series. In this respect we would differ from Shaw, who thought that corticoids might be of benefit, though he had not actually used them.

Surgical resection should be reserved for patients who have complete destruction of part of the lung, with gross bronchiectasis or continued suppuration. Occasionally resection will be necessary because of inability to make a preoperative distinction from a life-threatening lesion such as bronchial carcinoma. The widespread focal nature of the bronchiectasis in Case III, the apparent recovery of function which may occur if the obstruction does not persist for too long, and the hazard of thoracic surgery in asthmatic subjects are strong arguments against elective surgical intervention early in the course of the disease.

CONCLUSIONS

The evidence available suggests simply that asthmatic subjects have a quantitative or qualitative abnormality of bronchial mucus secretion.

From time to time this mucus obstructs bronchioles and bronchi. This complication may occur acutely during a paroxysm of asthma and be so widespread that death occurs. On the other hand, it may be ingravescent in its onset, localized to one or more segments and, for a time at least, clinically silent. Extreme atelectasis or infection usually leads to symptoms.

All grades of illness, from asymptomatic infiltrations of a few days' duration to complete obstruction of large bronchi with destruction of the related lung, have been described. The end result is represented by the surgical specimens Shaw has described. The clinical observations made here suggest that the course

of the disease may be a very long one, and it is not certain even when saccular bronchiectasis has developed that ultimate loss of lung tissue is inevitable.

ADDENDUM

Since the completion of this paper two further patients have been seen who illustrate well the natural history of the pulmonary changes and confirm the conclusions we have drawn above.

CASE VI.—A patient of Dr. M. R. Joseph was a fifty-two-year-old woman who had suffered from chronic asthma for many years. During the past fourteen years she had attended several thoracic clinics in Sydney for a series of radiological lung infiltrates. These infiltrates appeared at various times in all lobes of each lung, but were more marked in the upper lobes. No firm diagnosis was ever made. In September, 1955, she coughed up a number of firm plugs of mucus. A white cell count at that time showed a total of 18,000 leucocytes per cubic millimetre, of which 19% (3420) were eosinophile cells. A bronchogram in October, 1956, showed saccular bronchial dilatations in all lobes, most marked in the apical branch of the right upper lobe and the lower branch of the lingula. The right middle lobe was currently the site of one of these " infiltrates " and failed to fill with the opaque dye.

CASE VII.—L.G., aged twenty-three years, a dentist, gave a history of recurring attacks of asthma, usually associated with bronchitis, for most of his life, though less frequently since adolescence. He had felt off-colour with influenzal symptoms for five days before seeking medical advice on September 2, 1956. He then had a pain in the left side of his chest, a short dry cough and a temperature of 102° F. Crepitations were heard in his left axilla, and a diagnosis was made of pneumonia. A chest X-ray examination confirmed this, revealing consolidation involving mainly the lingula. From his sputum was obtained a mixed growth of organisms, reported sensitive only to " Aureomycin " and " Chloromycetin ". His total leucocyte count was 12,400 per cubic millimetre, of which 63% were neutrophile cells and 7% eosinophile cells (868 per cubic millimetre). Despite antibiotic therapy he remained febrile, and when he was seen in consultation by one of us (C.H.) on September 11, the clinical signs and chest X-ray appearances had not altered. However, he had lost his pain and cough. It was considered that there might be some bronchial block, and appropriate chest percussion by a physiotherapist was ordered. One week later, fever and signs persisted, but he now had a cough, which had resulted in the expulsion of a small plug of mucus on the previous day.

His chest X-ray film of September 18, 1956, showed some increase in the extent of the opacity. Within it, at least one clear-cut rounded " coin " shadow could be seen, and there were others in the left hilar region which appeared to be enlarged lymph nodes. The radiologist gave it as his opinion " that the picture was one of Hodgkin's disease or other malignancy ". This diagnosis was not accepted, an alternative one of mucoid impaction of bronchi was offered, and the physiotherapist was instructed to redouble her efforts.

During the next three days the patient coughed up several plugs which in his own words were " like marbles, tough, spheroidal and olive-green, one-quarter of an inch or so in diameter ". On the third day, after a heavy bout of coughing, there came a " sudden gush of greenish sputum, at least three-quarters of a cupful ". This apparently consisted of purulent, dammed-up secretion, released by the loosening of mucoid plugs. The temperature forthwith fell to normal, cough and sputum soon ceased, and further convalescence was uneventful.

Later X-ray examinations showed a rather slow but definite clearing of the opacity, which, as it resolved, left a pattern of cystic change. The last X-ray examination on October 19 showed a characteristic soap-bubble appearance in the left mid-zone near the hilum. By this time, however, the patient was symptom-free and back at work.

Comments

Case VI represents a very chronic form of mucoid impaction of bronchi. The patient has never been acutely ill in any of the episodes, and only recently has she been aware of coughing up mucoid plugs. However, it is felt that she has suffered multiple mucoid impactions over a period of at least fourteen years, that the eosinophilia is associated with chronic asthma rather than Loeffler's syndrome, and that the widespread saccular bronchiectasis (more marked in the upper than the lower lobes) represents the end-product of the repeated impactions.

In Case VII, the first episode of mucoid impaction in a known asthmatic led to an acute illness, diagnosed clinically as pneumonia, and almost reaching the stage of a lung abscess. The lumpy hilar opacities were misinterpreted by the radiologist as enlarged lymph nodes, and more sinister diagnoses were suggested. This patient, too, had a peripheral blood eosinophilia. An awareness of the condition of mucoid impaction led to a fruitful therapeutic attack by physiotherapy; and dislodgement of the mucoid plugs (apart from confirming the diagnosis) brought about resolution of the lesion. The cystic changes remaining in the left mid-zone as seen in the chest X-ray film suggest that bronchiectasis has already developed in this region.

Bronchiectasis, then, seems to have developed in at least six of our seven patients. In two it has been demonstrated surgically, in two it has been demonstrated by bronchography, and in two there are highly suggestive cystic appearances in the chest X-ray film. This bronchiectasis differs from the classical form in that it shows a predilection for the upper rather than the lower lobes, and the bronchiectatic saccules are far more proximally situated in the bronchial tree.

Eosinophilia in the peripheral blood has been seen in five out of the seven patients, of such a degree as to qualify the pulmonary changes for a diagnosis of Loeffler's syndrome in asthmatics by the standards of Crofton *et alii* (1952).

Finally, we believe from our recent experiences that mucoid impaction of the bronchus is a common disease in asthmatics, and that it is recognizable long before surgical interference is necessary for diagnosis or treatment. Relief of the bronchial obstruction leads to symptomatic improvement and probably prevents progressive destruction of the lung.

ACKNOWLEDGEMENTS

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THE PATHOLOGY OF ACUTE BRONCHIOLITIS—A STUDY OF ITS EVOLUTION

PART II: THE REPAIR PHASE[1]

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Le chemin est long du projet à la chose.
—Molière, *Tartuffe*, Act III, Scene 1, line 8.

SUMMARY

The histology of the repair phase of bronchiolitis is presented.

Evidence of old inflammatory damage to bronchioles was found in all lungs examined, except those of new-born infants. These changes were minimal in macroscopically normal lungs, and in these were more obvious in older patients than in the young. In the lungs in which macroscopic structural changes such as bronchiectasis, emphysema and scarring were present, bronchiolar damage was much more extensive. In all examples maximal changes were found in the region of the terminal bronchiole.

The evolution of these lesions was studied by observations on early changes, and the origin of some of the types of damage is suggested.

Complete obliteration of bronchioles was common, but not easily discernible. The factors influencing the ease with which the changes can be recognized are discussed, and it is concluded that such changes are much more common than has previously been indicated.

STANDARD descriptions of acute inflammatory disease of air passages imply, rather than state, that complete resolution is the expected outcome. While this may be true of the majority of lesions, the frequency of this *restituo ad integram* has been greatly overestimated. Incomplete resolution and even permanent obliteration of the smaller air passages is a common event, and not the curious rarity that descriptions such as those of Hart and Mayer (1928) and of Engel (1947) would suggest.

Although alterations in surrounding structures always accompany damage to bronchioles, observations in the present paper are restricted, as far as practicable, to the bronchiolar lesions alone; their relation to associated changes will be considered in subsequent papers.

The material examined has been described in Part I (McLean, 1956).

THE MORPHOLOGY OF THE DAMAGED BRONCHIOLE

With regard to the morphology of the damaged bronchiole, attention is directed principally to bronchioles exhibiting results of past inflammation; those showing acute inflammation or recent reparative change have been excluded.

General Features

All specimens examined, except those from new-born infants, showed evidence of old inflammatory damage to bronchioles. The least change was found in macroscopically normal lung tissue from children and young adults who gave no past history of severe respiratory illness. Branching of bronchioles was regular and essentially dichotomous, and even those tubes near the terminal bronchiole were usually structurally normal, but occasional scattered lesions in small bronchioles coldn always be found. In older patients in the same category there was more change, and in all such patients aged over forty years (however normal their lungs appeared to be on superficial inspection) diffuse damage to the smaller bronchioles was regularly found. When, in serial sections, bronchioles were traced peripherally towards the terminal bronchiole, slight irregular dilatations of variable length were found. The normal divisions of respiratory bronchioles frequently could not be identified; their walls were rarely complete throughout their length, and many were so altered as to be difficult to recognize. Abnormal

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communications with surrounding air spaces were seen mostly as defects in the walls of respiratory bronchioles, but also occasionally in those of terminal or preterminal bronchioles. These extensive structural changes in the region of terminal bronchioles, apparently occurring at random, were often associated with irregular thickening of the walls of neighbouring passages.

All these changes were accentuated in aerated lung tissue which showed such macroscopic evidence of damage as bronchiectasis or emphysema. Particularly in bronchiectasis many large bronchioles showed a gross thickening of the wall often affecting several divisions. Occasionally in emphysema and frequently in bronchiectasis, partial and complete obliteration of bronchioles was readily demonstrable.

In both conditions smaller bronchioles were often thin-walled and irregularly dilated, and their pattern of division was chaotic. When large bronchioles were traced peripherally, it became clear that the number of terminal bronchioles eventually reached was often considerably less than normal, and that the further one travelled peripherally, the more altered was bronchiolar structure. Bronchioles frequently divided into passages of considerably different diameter and length, and occasionally ended blindly.

Communications with peripheral air passages were abnormal. Usually the terminal bronchiole opened into a maze of intercommunicating and distorted air passages bearing little resemblance to respiratory bronchioles; but also there were sometimes direct communications with alveoli through defects in the walls of terminal or preterminal bronchioles. When these defects were large, the naming of "terminal" bronchioles became purely arbitrary.

The grossest changes were found in areas of chronic collapse or consolidation of the lung, such as apical lung scars and chronic "interstitial" pneumonia. Bronchioles entering such solid tissue were often dilated and thin-walled, but usually ended blindly just within the scar. Remnants of obliterated bronchioles could sometimes be traced further into the scar, but often the destruction was complete so that recognition was impossible; small bronchioles often terminated in a number of epithelial processes surrounded by masses of small round cells.

The Wall of the Damaged Bronchiole

Changes in the Components of the Wall. Whenever the lumen was patent an epithelial lining was present; usually this was normal, being pseudo-stratified and ciliated in the larger bronchioles, becoming non-ciliated and columnar in the terminal bronchiole and cuboidal or flattened in the respiratory bronchioles. Occasionally, however, small sharply demarcated areas of flattened epithelium were seen in bronchioles lined elsewhere by tall and even ciliated cells.

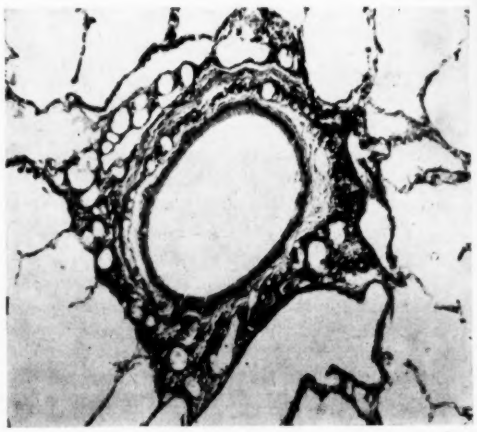

FIGURE I

Photomicrograph showing a large bronchiole in slightly emphysematous lung. The epithelium is separated from an irregular sub-epithelial elastic fibre net by vascular connective tissue. A group of muscle fibres is visible just outside this layer (upper left). Elsewhere there is some increase in the elastic fibres of the wall, some of which are continuous with those in the walls of adjacent air spaces. Numerous empty capillaries in the wall are conspicuous—this being due to intravenous fixation of the cadaver. Macroscopic examination of the lung revealed slight focal emphysema only. (Elastin stain, ×70)

In contrast, patchy loss of bronchiolar smooth muscle and elastic tissue was common even in macroscopically normal lungs. Muscle was more obviously affected, but detailed examination always disclosed at least slight alteration of and defects in the normally regular sub-epithelial elastic fibre net. In more severely damaged lungs, sometimes only occasional fibres of smooth muscle remained in a length of bronchiole (Figure I); some such bronchioles were thin-walled and dilated. Obvious loss of elastic tissue was seen mainly in thick-walled large bronchioles and in those with extensive obliterative changes; dilated

passages, particularly those with thin walls, usually had an intact, if somewhat irregular, sub-epithelial elastic tissue net.

Increased amounts of muscle were seen often in bronchiolar walls in the lungs of patients who had had prolonged asthma, but were less evident in the more damaged bronchioles than in those showing little evidence of past inflammation. Increase of muscle was found only in asthmatic patients; in general, the degree of muscle loss correlated well with the degree of change in the bronchiole.

However, elastic tissue, was sometimes distributed indiscriminately in relatively increased amounts. In bronchioles larger than preterminal size, this was seen in the outer part of the wall, the fibres often being continuous with those of the surrounding air spaces. Such formations were most commonly seen in emphysematous lungs (Figure I). In any lung, it was usually possible to find near a terminal bronchiole masses of elastic and muscle fibres which clearly represented residual tissues of adjacent respiratory bronchioles, whose walls had broken down. When such masses were related to the terminal bronchiole an appearance of thickening of the original wall was produced.

Particularly in bronchiectatic, but also in emphysematous, lungs the walls of the larger bronchioles were often thickened. These walls rarely contained more than a few muscle cells or isolated elastic fibres, the tissue being largely collagenous with masses of lymphocytes or even lymph follicles embedded in it. In some, obliterated remnants of other bronchioles and their vessels could be demonstrated in the connective tissue of the wall.

Completely obliterated bronchioles rarely contained significant amounts of specialized tissue. Usually the bronchiole was represented by collagenous tissue containing occasional elastic fibres and, less often, isolated groups of muscle cells. In a few instances, large bronchioles were represented by epithelial structures in the scar tissue; such isolated masses were occasionally cystic, containing mucus. Less frequently still, cords of epithelial cells were observed, continuous with the lining of the parent bronchiole and extending some distance peripherally.

Defects in Wall Structure. In lungs with minimal damage it was usually possible to reconstruct accurately the arborizations of the passages branching from the terminal bronchiole. In some of these lungs occasional defects in the walls of the smallest bronchioles were seen, by which the bronchiolar lumen communicated directly with the surrounding air spaces (which were also supplied by normal channels). These communications, absent from lungs of infants and children showing no significant evidence of past damage, were regarded as secondary.

The size of the lumen of these communications varied, but was usually less than that of the bronchiole itself. Some were simple defects in the wall (Figures II, III, IV), whereas others were slender and tortuous. Examination of the wall adjacent to the defect often showed loss of muscle (Figure IV), irregularities in the elastic tissue and, sometimes, some fibrosis. The epithelium lining the passage was sometimes attenuated and flattened (Figures II and IV), but in others it corresponded to that lining the bronchiole (Figure III); in both cases epithelium commonly extended over the adjacent surface of the air space into which it opened (Figure II).

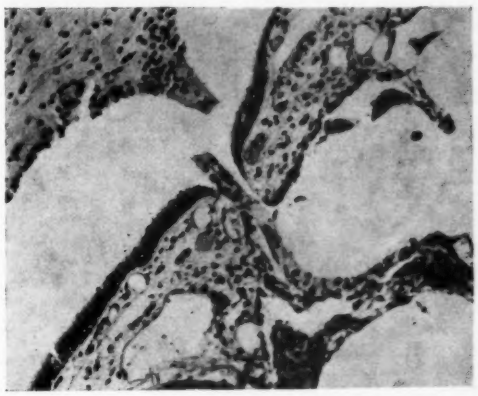

FIGURE II

Photomicrograph showing a small defect in the wal of a bronchiole three divisions proximal to the terminal bronchiole. The mucus plug in the lumen (upper left) has shrunk, but clearly had been continuous with an extension through the wall where most mucus has been phagocytosed. An irregular epithelium lines part of the wall of the space entered by the "secondary communication". On macroscopic examination the lung tissue was structurally normal; on microscopic examination bronchiolitis was present. (Hæmatoxylin and eosin stain, ×150)

At other sites in lungs showing these communications related changes were common. The wall of the bronchiole was occasionally formed only of epithelium, which often spread over the wall of the adjoining air space (Figure V). Similarly, localized thinning of the bronchiolar wall was seen, sometimes associated with diverticulum formation

(diverticula were also observed in the walls of the largest bronchioles, when they were similar in appearance to simple glands in the smallest bronchi). The changes described above were limited largely to the last three orders of bronchioles.

In lungs showing greater damage, structures of similar morphology were also seen; but distinction from altered original passages could not be effected owing to the damage and gross distortion of the peripheral air passages.

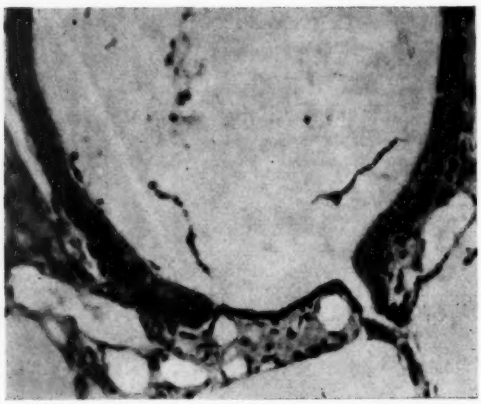

FIGURE III

Photomicrograph showing a preterminal bronchiole lined by ciliated columnar epithelium except at one site near a "secondary communication", which is partly plugged by a fragment of exudate and is lined on one side by columnar cells. The lung appeared normal on macroscopic examination. (Hæmatoxylin and eosin stain, ×250)

THE EVOLUTION OF CHANGES IN BRONCHIOLAR STRUCTURE

Some evidence of past damage was found in all lungs examined except those of new-born infants. Recent reparative changes, on the other hand, were uncommon, and in many cases opportunity arose only occasionally to study the complete sequence of changes leading to the results already described.

These changes will be presented under two headings: first, the changes in the bronchiolar wall, and secondly, the changes within the lumen.

Changes in the Bronchiolar Wall

The Tissues of the Wall. The rapid regeneration of epithelium following destruction such as results from viral or staphylococcal infection has been described in Part I of this study (McLean, 1956).

Dissolution of both muscle and elastic tissue occurred less rapidly than that of epithelium, and was seen clearly only in acute bronchiolitis when, for instance, as in staphylococcal infections, there was necrosis of the wall. In non-specific bronchiolitis necrosis of the wall was not seen in the acute stage, so that the argument that the loss of smooth muscle and elastic tissue seen in damaged bronchioles occurs only in specific infections is difficult to refute. However, the regularity with which these lesions were seen and their wide distribution leaves little doubt that prolonged non-specific infections can produce this result.

Increase in these elements was observed in some bronchioles. Thickening of walls of bronchioles has been observed to occur, as was mentioned earlier, by accretion of surrounding structures onto the original wall. This has resulted either from compression of the peribronchiolar air passages (seen in emphysema) or by collapse and subsequent organization of surrounding structures following spread of the inflammatory process.

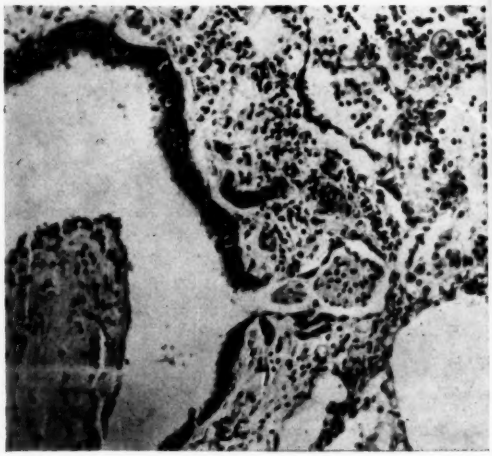

FIGURE IV

Photomicrograph showing a "secondary communication" through the wall of a medium sized bronchiole which is acutely inflamed. The path is somewhat irregular, and it is clear that mucus has spread into the adjacent spaces which contain macrophages and polymorphonuclear leucocytes (same case as in Figure II). (Hæmatoxylin and eosin stain, ×180)

Large bronchioles in aerated lung sometimes showed this sequel of inflammation on a larger scale; residues of obliterated bronchioles and vessels, together with condensed and organized lung tissue that originally separated these structures from the patent bronchiole under

examination, merged with it to form the extraordinary thick walls.

These observations suggest that significant regeneration of smooth muscle and elastic tissue does not occur in damaged bronchiole. However, it was sometimes possible to recognize within the lumen of bronchioles, tissue that was entirely inflammatory in origin. Where this tissue had become epithelialized, newly-formed

FIGURE V

Photomicrograph showing part of the wall of a damaged preterminal bronchiole. The adjacent space is lined in part by low columnar epithelium, which is continuous with that of the bronchiole through a small defect in the connective tissue of the wall (shown here at its maximum diameter). The lung appeared normal on macroscopic examination. (Hæmatoxylin and eosin stain, ×270)

fine elastic fibres could occasionally be seen immediately beneath the new epithelium. No similar conclusive evidence of new formation of smooth muscle was observed.

Defects in Wall Structure. Localized ulcerative lesions were noted in the exudative phase of acute bronchiolitis (see Part I). No secondary communication which was obviously of recent origin was observed, although some walls were lined by most attenuated epithelium. In two cases in which there was proximal obstruction by an endo-bronchial neoplasm, secondary communications were peculiarly abundant in the smallest bronchioles (as were related changes). In one case in which intravenous fixation was used, there was extensive plugging of bronchioles with mucus, and the consequent acute bronchiolitis. At the sites of the communications mucus had flowed through the defect in the wall and had been phagocytosed (Figures II and IV), suggesting that a relatively high intrabronchiolar pressure had existed before death. The surrounding air spaces were not dilated.

In both lungs some of the secondary communications were narrow and tortuous and, when they communicated with the surrounding air spaces, they were often enveloped by aggregations of lymphocytes. In others, the passage from the bronchiole ended blindly in a mass of lymphocytes, and the adjacent spaces were lined with epithelium. In yet others, when the structure was sufficiently normal to exclude the possibility of confusion with obliterated bronchioles, thin cords of epithelium were traced from the bronchiolar lining, through lymphocyte aggregations to become continuous with epithelium lining adjacent spaces (Figures VI). Much more commonly, completely

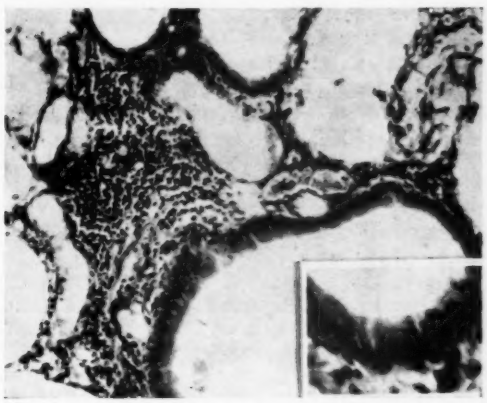

FIGURE VI

Photomicrograph showing part of a small bronchiole with an aggregation of lymphocytes containing prominent capillaries in its wall (centre). Muscle and elastic tissue are absent from the bronchiolar wall at this site. Two spaces (above) related to the lymphocyte aggregation are lined by epithelium, that on the right being, in part, columnar (see inset, ×280). The lung appeared normal on macroscopic examination. (Hæmatoxylin and eosin stain, ×120)

isolated areas of epithelium were found lining small areas of air spaces adjacent to collections of lymphocytes in the outer parts of walls of bronchioles.

Changes Within the Bronchiolar Lumen

The condensation of elastic tissue which in a normal bronchiole forms a dense network

immediately beneath the basement membrane of the epithelium is clearly seen with good elastic tissue stains. This layer was a most useful point of reference in the damaged bronchiole since, when changes had occurred within the lumen, it indicated the original site of the epithelium. By the utilization of this feature, it was possible to show that bronchiolar obliteration occurs by two processes: (i) by organization *in situ* of material occluding the bronchiole; (ii) by bronchiolar "collapse" following absorption of inflammatory products in the lumen. Obviously, both processes may occur simultaneously, and intermediate forms are common.

Organization in situ. When organization *in situ* occurs, the material retained in the lumen is invaded by fibroblasts and capillaries. The wall structures, if they have not been destroyed, maintain their normal orientation and often call attention to the original lumen. Both partial and complete occlusion by this process were observed at all levels, from the respiratory bronchioles even to small bronchi; but the region of the terminal bronchiole was much more often affected than the larger passages.

On occasions, organization of the material in the lumen was observed at sites where the original epithelium was no longer present. In some of these examples, the plug had been expelled and an irregular thin layer of newly formed epithelium had covered the granulation tissue. In older lesions, a layer of vascular connective tissue was seen separating the surviving sub-epithelial elastic net from epithelium indistinguishable from that in unaffected areas. This occurred either in small areas of the bronchiolar wall or over the whole surface for a considerable length (Figure I). Thus partial occlusion may follow acute bronchiolitis if the plug is retained sufficiently long. Extensive changes of this type frequently involved larger bronchioles in bronchiectasis. Clear recognition obviously depends on the survival of the sub-epithelial elastic tissue and therefore on elastic tissue stains. Hart (1908) illustrated a good example of this type of change in a case of atypical pneumonia, while less obvious forms were shown by Spain and Kaufman (1953) and by Reid (1954).

In general, significant narrowing of the lumen by this process is uncommon in small bronchioles; when examples were found, it was possible to demonstrate that there were, in the same area, many more completely obliterated bronchioles.

The evolution of complete obliteration by "organization *in situ*" was followed with relative ease in tissue from two cases of uræmia in which the bronchioles were obstructed by blood clot, and in which the process was not obscured by an intense cellular reaction. In these cases there had been repeated intra-pulmonary bleeding and hæmoptyses in the weeks preceding death.

Most of the larger bronchioles were empty except for some containing fresh blood clot, whereas most terminal bronchioles and first order respiratory bronchioles were occluded by material varying from fresh blood to well-formed granulation tissue. Beyond the respiratory bronchioles, the terminal air passages and alveoli usually contained air and scattered masses of red cells or macrophages packed with blood pigment (Figure VII).

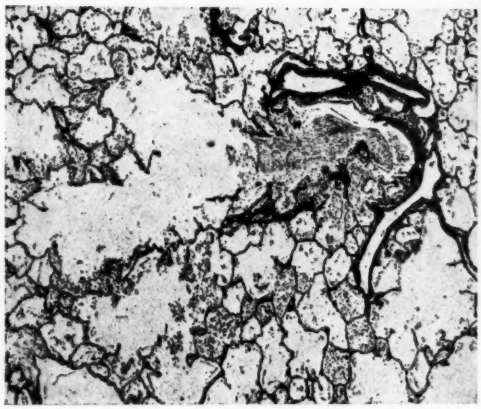

FIGURE VII

Photomicrograph showing a second order respiratory bronchiole (right) and part of its arborization (to the left). Young granulation is present in the lumen of the respiratory bronchiole and its immediate branches, but more peripheral passages contain only scattered red cells. Foci of firm, pale tissue were obvious macroscopically. The case was one of uræmia. (Elastin stain, ×15)

In the region of the terminal bronchiole, the earliest changes observed after occlusion by clot were loss of red cell structures and the accumulation of occasional polymorphonuclear leucocytes in the clot, followed by the appearance of macrophages. Ground substance staining with Alcian blue formed around some of the macrophages; subsequently the cells became spindle-shaped (Figure VIII), and at many sites reticulum appeared between them.

Although epithelium was absent from the wall wherever the granulation tissue was continuous with the submucosal connective

tissue, no direct evidence of necrosis of epithelial cells was apparent anywhere in lesions showing various stages of the process.

Similar examples of organization *in situ* were observed in various forms of acute bronchiolitis, but were particularly evident in the bronchiolitis associated with fibrocystic disease of the pancreas and also, to a less extent, in prolonged asthma. Both these conditions are characterized by extensive bronchiolar occlusion with tenacious mucus. In fibrocystic disease, organization of the peculiarly viscid mucus has been observed in the bowel (Williams, 1955); but similar changes in the bronchioles have not previously been recorded.

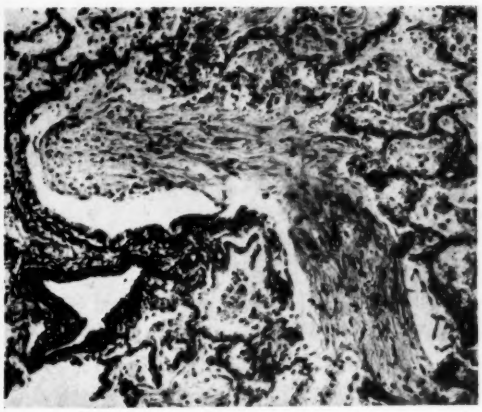

FIGURE VIII

Photomicrograph showing a bronchiole, similar to that in Figure VII, cut through part of its arborization. A plug of granulation tissue is seen in the lumen and adjacent alveoli, but has stripped off the walls at most sites, partly as a result of endobronchial fixation and partly by shrinkage. In the fresh specimen such areas were solid (same case as in Figure VII). (Elastin stain, ×90)

In three subjects of terminal staphylococcal bronchiolitis in fibrocystic disease that were examined, intraluminal organization in bronchioles was extraordinarily prominent. The respiratory bronchioles, particularly of the first and second orders, were most often affected; there was progressively less change in larger air passages. Without elastic tissue stains to delineate the bronchiolar walls, early organization of the material in the lumen could not be positively recognized (Figure IX); but it was an easy matter with such staining (Figures X to XIII). Persistence of the plug resulted in continuing organization (Figure XI) and led to complete occlusion of respiratory bronchioles (Figures XII and XIII) or terminal bronchioles (Figure X). The inflammatory process was often restricted to these bronchioles, and in such cases, collateral ventilation maintained aeration of the more distal air passages (Figures XI to XIII).

Bronchiolar Collapse. Sometimes absorption of the plug is followed by collapse of the bronchiolar wall and reduction of the lumen. Ordinarily, partial absorption of the plug aids the expulsion of the remainder by homœstatic mechanisms; however, if, these mechanisms are inadequate, and if the forces acting to expel the plug and incidentally dilate the bronchiole are less than those tending to cause it to collapse, the passage becomes reduced to a thin, distorted cord or ribbon, and the lumen is organized with minimal formation of new tissue.

In aerated lung, this type of change was seen predominantly in first or second order respiratory bronchioles, the change occasionally extending one or two divisions proximally. In non-aerated lung, it sometimes extended further proximally into larger bronchioles.

Occlusion of terminal bronchioles and their immediate branches by inflammatory exudate was most readily appreciated in the lungs of children and young adults. In some of these cases plugs appeared to have been largely absorbed and the original lumen reduced to a narrow, distorted passage filled with inflammatory exudate, leading peripherally to aerated spaces (Figure XIV). In some examples, a single division of a terminal bronchiole remained occluded (Figure XV); in such cases, with organization of the passage and epithelialization of the bronchiolar surface of the occlusion, it was clear that little evidence of the obliterative event would remain.

In older patients the same phenomenon was seen in previously damaged bronchioles. Often, the lining of the occluded air passage was irregular; transition from cuboidal epithelium to cells indistinguishable from macrophages was common (Figure XVI). In many of these cases in which bronchiolitis with bronchiolar "collapse" was seen, the inflammation appeared to be due to non-specific organisms, and necrosis of epithelium was not observed.

Old lesions possibly due to this type of obliteration were occasionally seen. Some partially occluded passages in the region of terminal bronchioles exhibited condensation and irregular folding of the sub-epithelial elastic tissue net, which suggested that the lumen had been cleared before obliteration was complete.

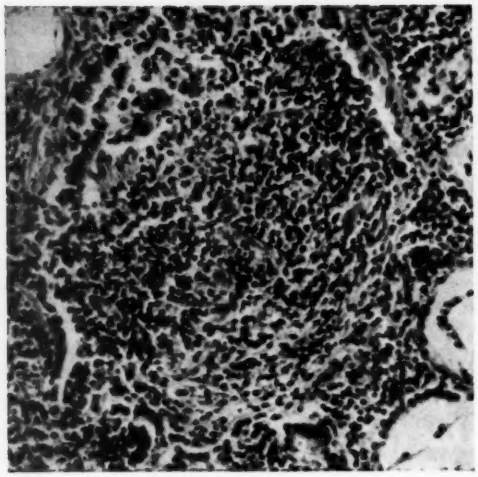

FIGURE IX

Photomicrograph showing an ill-defined terminal bronchiole cut transversely and occupying most of the illustration. The plug in the lumen was in the process of organization (from the lower right). The case was one of fibrocystic disease of the pancreas; staphylococcal bronchiolitis. (Hæmatoxylin and eosin stain, ×180)

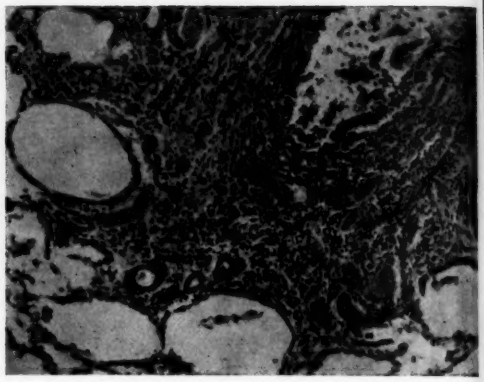

FIGURE X

Photomicrograph showing a bronchiole (upper right) with considerable recent organization of the original lumen, which is indicated by the surviving elastic tissue in the wall. All its branches were completely occluded, and the adjacent spaces were lined by epithelium, often showing small epithelium-lined recesses (lower right). The case was one of fibrocystic disease of the pancreas.—(Elastin stain, ×100)

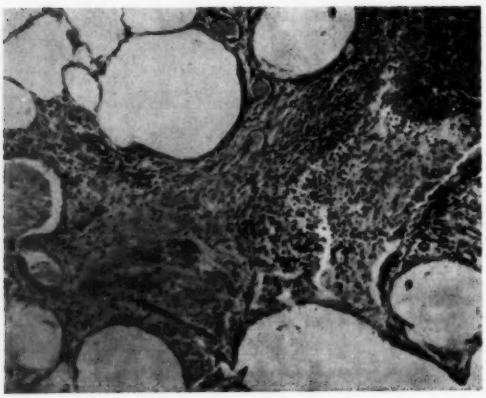

FIGURE XI

Photomicrograph showing a respiratory bronchiole (entering from upper right) containing exudate and polymorphonuclear leucocytes. One branch (lower right) is merely filled with exudate, but granulation tissue has occluded the lumens of the remainder. The case was one of fibrocystic disease of the pancreas. (Elastin stain, ×100)

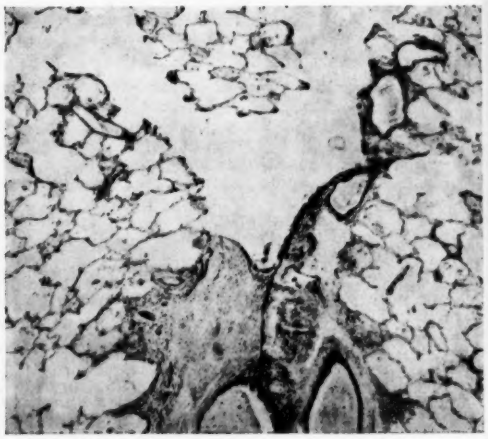

FIGURE XII

Photomicrograph showing granulation tissue completely occluding a second order respiratory bronchiole, more peripheral passages being aerated. The distal surface of the plug has been epithelialized. The original lumen is clearly outlined by surviving elastic tissue. The case was one of fibrocystic disease of the pancreas. (Elastin stain, ×25)

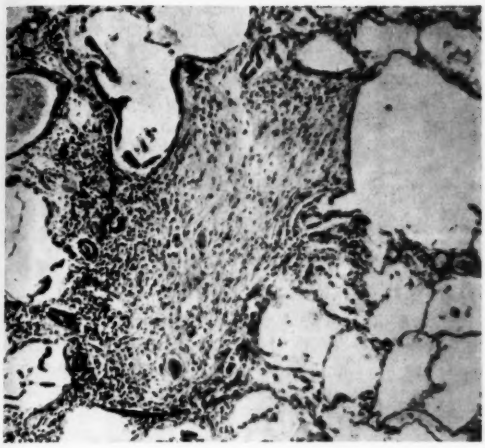

FIGURE XIII

Photomicrograph showing an organized plug in the lumen of a (second order ?) respiratory bronchiole, with epithelialization of the distal surfaces. The case was one of fibrocystic disease of the pancreas. (Elastin stain, ×100)

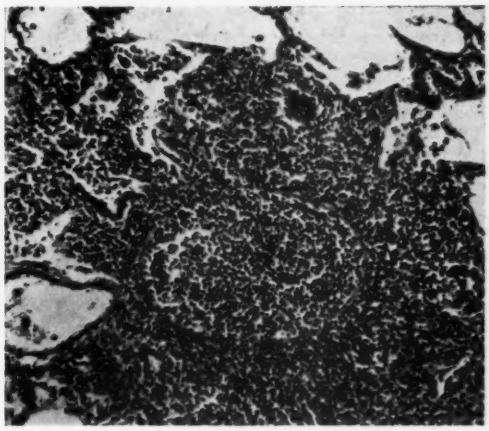

FIGURE XIV

Photomicrograph showing a terminal bronchiole (centrally). The bronchiole and surrounding tissue are involved in extensive acute inflammation. The bronchiolar wall is absent over a small area (above); the exudate in the lumen was continuous with that in narrow, distorted and epithelium-lined passages (upper left). The case was one of bronchiolitis in an infant. (Hæmatoxylin and eosin stain, ×70)

FIGURE XV

Photomicrograph showing a dilated terminal bronchiole with an obvious deficiency in the wall (above) filled with cellular exudate, and continuous, on another plane, with the air-containing spaces above. Reconstruction left little doubt that this represented a distorted respiratory bronchiole (with dissolution of all its elastic tissue in the affected area). The case was one of bronchiolitis in a child. (Elastin stain, ×80)

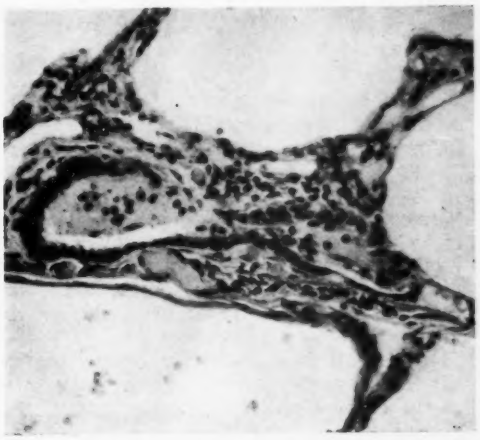

FIGURE XVI

Photomicrograph showing a bronchiole containing a mucus plug (left), with a branch communicating with an air space (right). The branch is shown at its greatest diameter. The epithelium of the passages is irregular, with macrophages lining part of the distal end of the branch. The mucus plug ends sharply where the branch opens into the dilated air space (right). The case was one of terminal bronchiolitis in an elderly man. (Hæmatoxylin and eosin stain, ×180)

The Recognition of Obliterated Bronchioles

Amongst the results of past inflammation, completely obliterated bronchioles proved the most difficult to detect. Most that were found subsequently were overlooked in the initial examination and reconstruction of the sections; certainly many more might have been found with further reexaminations.

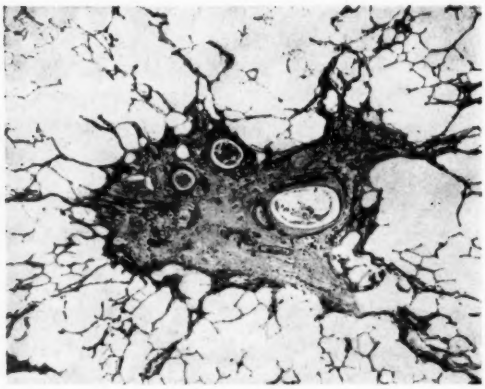

FIGURE XVII

Photomicrograph showing an old obliteration of a first order bronchiole. A few arteries remain in the mass of scar tissue, which contains elastic tissue only on its periphery. The case was one of asthma with moderate emphysema in some areas. (Elastin stain, ×14)

The factors that influenced recognition of such obliterated bronchioles included the following:

The State of the Surrounding Lung

In collapsed and scarred lung, reconstructions of the original arborizations of damaged bronchioles was usually impracticable, and often in such scarred areas even obliterated branches of large bronchioles could not be identified.

In aerated lung, however, the recognition of the original pattern of branching was rarely effected with facility, because of the accompanying distortion and disorganization of the surrounding air spaces. In bronchiectasis and emphysema even obliterated bronchioles that were originally large were easily overlooked (Figure XVIII).

The Size of the Bronchiole Affected

Where an obliterated bronchiole was found, all its divisions as far as and including the respiratory bronchioles were similarly involved. Thus in one case of prolonged asthma the whole distribution of a first order bronchiole was obliterated, and the lesion could be traced macroscopically from its origin in the wall of a dilated bronchus to the periphery (Figure XVII). Such examples were rare.

The smallest old obliteration positively recognized was a preterminal bronchiole and its distribution. Isolated old obliterations of terminal and respiratory bronchioles were sought, but were never proven.

The Density of the Lesions

An isolated example was usually obvious, but more often there was, in one area, a large number of obliterative lesions affecting bronchioles of all sizes. Three-dimensional reconstruction usually permitted recognition of multiple lesions affecting larger bronchioles; but in more damaged lungs this was usually impracticable, particularly with smaller bronchioles. In macroscopically normal lungs from old patients a first division bronchiole

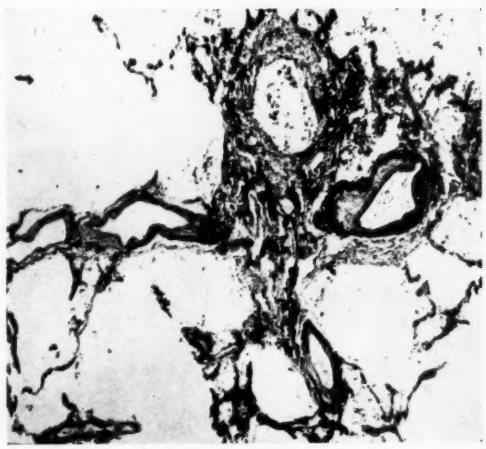

FIGURE XVIII

Photomicrograph showing a severely damaged medium-sized bronchiole with its attendant artery (upper right). No bronchioles accompany the branches of the artery (below and left), but a cord of granulation tissue ran from the bronchiolar wall to join the arterial branches and became related to distorted peripheral passages. Part of this cord and its relation to a peripheral passage is shown (centre, below). The case was one of emphysema with bronchiolitis. (Elastin stain, ×30)

was often found to end in less than five communications with terminal air passages. Originally there must have been 40 to 100 terminal bronchioles (Hayward and Reid, 1952), and although there was often evidence

of extensive obliteration, the alterations in architecture were such that an accurate conception of the pattern of bronchiolar obliteration could not be obtained. However, that this process had occurred extensively could not be denied.

The Relations of the Residual " Scar "

The process of complete occlusion necessarily involves the formation of some granulation tissue in which, later, collagen matures to form a " scar ". The presence of this tissue in relation to broncho-vascular bundles therefore raised suspicion that obliterative processes had occurred. An obliterated large bronchiole was often recognized by a cord of connective tissue, which could be traced peripherally in serial sections from a damaged area in the wall of the parent bronchiole. From this area the cord often ran outside the wall of a surviving bronchiole for a short distance, divided repeatedly, and became so closely related to accompanying pulmonary arterial branches that the connective tissue cords had the appearance of " peri-arterial fibrosis ". Further peripherally, these cords, accompanied by pulmonary arterioles, ended amongst terminal air passages, which did not take origin proximally from patent bronchioles, but which were aerated by adjacent lobules (Figure XVIII).

These connective tissue cords frequently contained small masses of black pigment, both within macrophages and lying apparently free. Young connective tissue was vascular (Figure XVIII), but in older tissues with well formed collagen few capillaries were seen, and the scar was much reduced in size (and therefore less obvious); nevertheless the pigment granules remained.

Obliterated Secondary Communications

As has been indicated, various unusual structures were found in the walls of smaller bronchioles. Certain of them were related structurally to secondary communications and appeared to have arisen by obliteration of such defects, probably by the same processes as bronchioles themselves are obliterated.

Only in the most normal lungs was it possible to show that these were not obliterated small bronchioles; in lungs exhibiting distortion of the surrounding air spaces, distinction between the two could not be effected. This confusion, therefore, was an important factor in preventing positive recognition of examples of old obliterative processes confined to the smallest bronchioles.

The Extent of Damage to Wall Structure

The survival of any of the specialized tissue in the wall of the obliterated bronchiole aids greatly in its identification. When muscle and elastic tissue survived in any demonstrable amount, definite identification of the bronchiolar origin of the scar was usually possible. In the smaller bronchioles positive identification generally required the survival of enough elastic tissue to permit reconstruction of the original form. However, very often, these tissues could not be recognized in an obliterated bronchiole that had been identified by other means.

Occasionally epithelium may survive in the obliterative process. The most remarkable form was a solid cord of epithelial cells extending along the length of the obstructed bronchiole; but examples of this were found only in bronchiectatic lungs. Watts and McDonald (1948) illustrate a good example, also in a case of bronchiectasis. Occasionally in less damaged lungs, epithelium could be traced for a short distance from the site of origin of the scar, only to disappear. Rarer phenomena were an isolated nubbin of epithelium or a small mucus-containing cyst in the scar.

Although epithelium was present only occasionally in the scar, it frequently lined the air spaces about which the scar terminated. As these " alveoli " could often be recognized in reconstructions to be the distal divisions of respiratory bronchioles, this epithelium could be regarded as having reformed over the distal end of the occlusion (Figures X, XII and XIII).

In such formations the epithelium was not continuous with that lining bronchioles. This feature led to examination of damaged lungs for epithelium in unusual sites.

One commonly observed form, unrelated to obliterative changes, was an epithelial layer on the walls of peripheral air passages containing fluid, and was seen well in chemical and viral pneumonia; however, it did not persist with resolution and reaeration.

The second type was seen in aerated lung in which there was no evidence of recent change. Isolated areas of epithelium, usually cuboidal but sometimes columnar in form, were found lining spaces and overlying aggregations of connective tissue. In a few cases this led to the recognition of obliterated bronchioles, the epithelium having grown over the distal end of the occlusion; yet in most examples this mode of formation could not be demonstrated, and indeed in some cases could be positively excluded.

Isolated areas of epithelium, occurring in sites unrelated to obliterated bronchioles,

included those already described as possibly being derived from occluded secondary communications, and were often related to aggregations of lymphocytes in the bronchiolar wall. Another type comprised those overlying accumulations of pigment-filled macrophages or masses of pigment-containing scar tissue in peripheral passages.

The most obvious form in which epithelium was found isolated from the bronchiolar lining was that seen in relation to damaged, thick-walled bronchioles in bronchiectatic lung, in which the adjacent air spaces were lined with epithelium on that part of their surface formed by the bronchiolar wall. In some cases, most of the outer surface of the bronchiole was epithelialized. Although the surounding spaces were invariably distorted, it was sometimes possible to reconstruct branching air passages apparently arising from the bronchiolar wall.

As the affected bronchiole regularly showed evidence of considerable damage and reduction of its divisions, and as occasionally remnants of obliterated bronchioles could be seen forming the outer layers of the wall, at least part of this change could be accounted for by bronchiolar obliteration and epithelialization of the surfaces at the distal end of the occlusions.

Discussion

In the course of this presentation various agents associated with bronchiolar inflammation have been mentioned; these were viral, chemical or bacterial. However, it should be clear that the extent and type of permanent change are determined more often by alterations in host factors than by any variability of the agent itself. These host homœostatic factors have been discussed in Part I of this paper (McLean, 1956), and emphasis has been placed on the significance of retention of plugs of material occluding the lumen in which bacteria may proliferate and so prolong the inflammation. Thus, although extensive bronchiolar obliteration may occasionally follow gross initial damage, usually the initiating agent is one which does not ordinarily produce significant permanent damage (for example, the influenza virus), and in most such cases failure of homœostasis with retention of plugs and secondary bacterial infection can be recognized. Examples used here include areas of collapsed lung, in which the plugs cannot be expelled without reaeration, and fibrocystic disease of the pancreas, in which the mucus forming the plugs is peculiarly viscid.

This should emphasize the importance of host homœostatic mechanisms in limiting damage and of secondary bacterial infection as a major factor in the production of bronchiolar damage and obliteration.

It would be expected, therefore, that patients who gave no history of severe respiratory infections would show the least change in their bronchioles. This was found to be so; but even in these patients, although the lungs of many were macroscopically normal, relatively slight but extensive lesions were found, increasing with age.

Thus it must be concluded that these lesions represent the cumulative effect of such common episodes as childhood viral infections, colds that lingered, influenza, "bronchitis" and inhalation of irritating material. Obviously, in any one incident, most inflamed bronchioles would resolve completely; but the tiny number permanently damaged becomes increasingly significant as similar episodes recur over the subsequent years.

The extensive distribution of permanent structural changes in bronchioles due to past inflammation has not been previously stressed. Changes were found in all adult lungs examined, and in any one example, evidence of damage became increasingly apparent as bronchioles were traced peripherally, the greatest change being seen in the region of the terminal bronchiole.

These changes included obliterative processes, which often result in permanent complete occlusion of the bronchiole. Study of the early evolution of bronchiolar obliteration indicated that the terminal bronchiole and its immediate branches were most often affected; but in older lesions, obliterations involving less than three divisions of bronchioles were never positively recognized. Remnants of the largest bronchioles were difficult enough to recognize even with three-dimensional reconstruction, and even in examples in which there obviously must have been extensive obliteration of small bronchioles, no evidence of their original structure was found. It is obvious, from a consideration of the factors influencing recognition of these obliterated passages, that such changes in the region of the terminal bronchiole may, with the passage of time, become inconspicuous if not imperceptible. Thus, the disproportionately small numbers of old lesions demonstrated directly in the region of the terminal bronchiole do not influence the proposition that obliterate changes are common in the lung and are maximal in the smallest bronchioles.

However, even the number of obliterated bronchioles of relatively large size that were

directly demonstrated makes it clear that this change is far commoner than is usually supposed. Study of obliterative bronchiolitis has been, in the past, almost entirely restricted to a rare and obvious form known as *bronchiolitis obliterans*. This is characterized by occlusion of most bronchioles (and even small bronchi) by granulation tissue. This extreme expression of the condition has been observed most often following virus disease of the respiratory tract complicated by secondary infection (Hart, 1908; Hübschmann, 1916) and exposure to toxic gases (Groll, 1921; Miller, 1922; McAdams, 1955). As it is unusual for a patient to survive gross necrotizing bronchiolitis, to die subsequently only two to six weeks later, it is not astonishing that this form of the disease is rarely seen.

Although Hart and Mayer (1928) suggested that bronchiolar obliteration was probably much more common in less extensive forms, few authors mention having recognized evidence of it. Reid (1954) mentioned that it occurs in non-specific chronic bronchitis; but its evolution and the anatomy of older lesions have not been adequately described.

Even in exceptionally favourable material, few authors have recognized more than the most obvious examples of obliterated bronchioles. In cases of *bronchiolitis obliterans*, when clear examples were found elsewhere in sections, changes have been described which clearly represented missed examples. For instance, Dunin-Karwicka (1912) described sites in bronchiolar walls replaced by granulation tissue which extended out into the peribronchiolar area, while Hart (1908) observed that this tissue became periarterial further peripherally.

The responses of the specialized tissues of the bronchiolar wall to inflammation and the sequelæ of inflammation are poorly understood. Some aspects of this problem are therefore discussed where the observations made in this paper impinge on them.

Superficially, epithelial changes appear simple; the cells may be destroyed by chemical or viral agents or by ischæmia, but regenerate rapidly and soon present a normal appearance. However, in the small bronchioles, in which considerable lengths of the wall may be completely denuded, the source of the new epithelial cells is not clear.

Also, in non-specific infections epithelium is apparently undamaged; yet in several examples described above, epithelium disappeared rapidly in the obliterative changes of such infections. Observations strongly suggest that this occurs by metaplastic change of the epithelium into macrophages which, in some circumstances, differentiate further into fibroblasts.

This proposition would in the previous century have been surprising; but, since Waddell (1949) has shown that the epithelium of the bronchial tree is mesodermal in origin and rigid embryogenetic concepts are at last being abandoned, it is presumed that few would be disturbed by it today.

Metaplastic change to macrophages occurs rapidly in the flat and attenuated epithelial cells which have been shown to line normal alveoli (Bertalanffy and Leblond, 1955). There is now little doubt that the macrophages, so commonly seen in alveoli in inflammatory conditions, largely arise from these lining cells. Evidence supporting this has been adduced by many authors, such as Briscoe (1908), Sewell (1919) and Cappell (1929). More recently, in tissue culture (Schiller, 1956) and in experimental animals (von Hayek, 1952), it has been shown that the most effective stimulus inducing this change is increased acidity of the environment of the cells—a change well recognized to occur in inflammation.

Thus, if metaplasia of the alveolar lining is accepted, there can be little objection to hypothesizing a similar phenomenon in the related epithelium of the smallest bronchioles. Evidence of phagocytic metaplasia has been found even in ciliated epithelium in mice (Duthie, 1930), and few deny the predominantly epithelial origin of the phagocytic giant cells found in air passages in such conditions as measles, pneumonia—an origin proposed by Kromayer (1889), by Dunin-Karwicka (1912) and by others since (Wolman and Izak, 1952).

However, the epithelium of larger bronchioles may survive obliterative processes, either in continuity with that of the parent bronchiole or as isolated masses or cysts. These formations have interested many authors recently, and though the more bizarre forms have been thought neoplastic by some, Whitwell (1955), reviewing the subject, concluded that they were simply hyperplastic. Their relation to obliterative processes has not previously been indicated, although cords of epithelium continuous with the parent bronchiole have been illustrated by several authors, the reports of Watts and McDonald (1948) and of Spencer and Raeburn (1954) being particularly clear.

To consider isolated areas of epithelium lining peripheral air spaces, it is clear that some are the result of obliterative processes, either of bronchioles or of secondary communications. The source of the epithelium is puzzling in

those cases in which these origins can be ruled out; the probable sources are alveolar epithelium or metaplasia of macrophages.

Dissolution of elastic tissue and smooth muscle was obvious only in areas of necrosis, but almost certainly occurs slowly in prolonged non-specific bacterial infections. Regeneration and new formation of both elastic tissue and smooth muscle could not be demonstrated in the bronchiolar wall, but in the case of elastic tissue, definite evidence of new formation was seen in intraluminal tissue.

Abundant new formation of elastic tissue in organs other than the lung has been observed in scars in heart muscle (Bunting, 1939), in the aorta in lathyrism (Menzies and Mills, 1957), and in the thickened intima of arteries (Leriche and Froehlich, 1936). Thus the effective stimulus inducing elastic fibre formation in connective tissue would appear to be the repeated application of a stretching force of some magnitude.

Possibly, therefore, new formation would account for the surprising constancy with which sub-epithelial elastic tissue was found in thin-walled and dilated damaged bronchioles. On the other hand, as gross diminution of elastic fibres is common in thick-walled or obliterated bronchioles, it is clear that these structures do not receive stimuli adequate to induce new formation.

Acquired defects in the walls of the smallest bronchioles have received little attention previously. Lamble (1955) recently described "bronchiole-alveolar communications" in diseased lungs, but did not distinguish between grossly altered original passages (which most of her photomicrographs appeared to illustrate) and true secondary communications. She also observed this type of change in macroscopically normal lungs, and apparently found no young person's lung without them (and so regarded them as normal formations).

In the material presented here, true secondary communications were often surrounded by accumulations of lymphocytes. This association of epithelium and lymphocytes is a familiar one in the tissues of the neck and thorax (Heinz, 1950; von Hayek, 1952). However, it was clear that these passages could be obliterated, and so would account for some examples of epithelialization of air spaces related to bronchioles, and also for some of the diverticular found in the walls of bronchioles. Similar diverticular in small bronchioles were illustrated by von Hayek (1952), with others in the largest bronchioles in "normal" lungs.

The pathogenesis of all these structures is obscure. Most subjects exhibited evidence of inflammatory damage in the wall at the site of the defect, and the frequent occurrence of the structures in two cases, in which there was good evidence of raised endobronchiolar pressure in the presence of inflammation of the wall, hints that they may result as "blow-outs" in a weakened area of wall. The absence of any structural change in the surrounding air spaces argues against any stretching force having been exerted on the bronchiolar wall by distension of these spaces.

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MILD HÆMOPHILIA—A CLINICAL AND LABORATORY STUDY[1]

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SUMMARY

In a series of 65 patients suffering from hæmophilia (AHG deficiency), 19 (29%) were found to have a normal whole-blood coagulation time. These patients suffered from a mild form of the disease as assessed clinically and on the results of laboratory tests. Ages ranged from nine to sixty-seven years. Seventeen families were involved; in eight of these other members were affected.

Hæmorrhagic episodes were mostly related to periods when the hæmostatic mechanism was placed under stress, as after tooth extraction or surgical procedures. Spontaneous hæmorrhages and hæmarthroses were uncommon symptoms.

The whole blood coagulation time was normal in all 19 patients. The prothrombin consumption index was normal (0% to 40%) in 13 patients and borderline (20% to 40%) in seven. The result of the thrombin generation test was normal in 10 of 15 patients tested. The most reliable method for diagnosis was the thromboplastin-generation test. This test gave abnormal findings in 15 patients, and with a modification involving use of a greater dilution of plasma gave an abnormal result in all patients.

Plasma AHG concentrations have been measured in these patients, and the results confirm that at least 30% AHG is necessary for normal hæmostasis.

THE defect in blood coagulation in hæmophilia is an imperfect production of intrinsic plasma thromboplastin. Plasma thromboplastin is produced in blood allowed to clot *in vitro* by complicated reactions involving platelets and several plasma coagulation factors. A deficiency of one of two or possibly more of these plasma factors results in a similar defect in hæmostasis. It is only since 1952 that various types of hæmophilia have been distinguished as separate entities, and since that time differences of opinion have given rise to much confusion concerning nomenclature (Pitney and Dacie, 1955). Most British workers use the term hæmophilia not in a generic sense, but to indicate a deficiency of a specific plasma thromboplastin precursor substance, usually called antihæmophilic globulin (AHG). This is the manner in which the term is used in this paper.

The clinical severity of the hæmophiliac state is closely related to the degree of AHG deficiency. Severely affected hæmophiliacs are often disabled by repeated hæmarthroses and spontaneous hæmorrhages into muscles and from mucous membranes. The whole-blood coagulation time may be greatly prolonged. Traces only of AHG can be demonstrated in the plasma (Langdell *et alii*, 1953; Biggs *et alii*, 1955; Pitney, 1956*a*).

If the AHG deficiency is less marked, hæmorrhagic symptoms may become manifest only when the hæmostatic mechanism is placed under stress, as after tooth extraction or a surgical operation. The whole-blood coagulation time is frequently normal. Hæmophilia with a normal coagulation time is a well-recognized entity (Merskey, 1950*a*; Graham *et alii*, 1953; Fantl and Sawers, 1954; Pitney, 1956*b*), and such cases make up an appreciable percentage of any large series of cases of hæmophilia. The patients concerned form an interesting group, as their disease may go unrecognized in everyday life, and diagnosis is not possible without the aid of the more recently developed laboratory techniques. They undoubtedly form a considerable proportion of that group of patients who claim they are "bleeders", but in whom laboratory findings have previously been considered normal.

In this paper a series of 19 hæmophiliacs with normal coagulation times are studied from both the clinical and the laboratory aspects. In most of them the degree of AHG deficiency has been assessed, and their plasma AHG concentrations are correlated with the other findings.

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MATERIAL

Eighteen patients have been studied during the past eighteen months in the Department of Hæmatology, Postgraduate Medical School, London. One patient has been studied recently at the Royal Perth Hospital. As far as can be determined, none of these patients has previously been included in any published series of hæmophiliacs.

LABORATORY METHODS

Tests for bleeding time, capillary resistance, platelet count, Quick's one-stage test and plasma fibrinogen concentration were carried out by established methods (Dacie, 1956). These tests all gave uniformly normal results, and will not be further considered.

Whole-Blood Coagulation Time

Determination of whole-blood coagulation time was performed on venous blood by the method of Lee and White, as described by Biggs and Macfarlane (1953). Blood was collected into a siliconized syringe through a 19 S.W.G. needle, without air bubbles and without negative pressure in the syringe. Amounts of one millilitre were then transferred to four unsiliconized three inches by three-eights of an inch tubes already placed in the water bath at 37° C. The stopwatch was started at the moment blood first entered the syringe. The tubes were left undisturbed for five minutes and then tilted in succession at thirty-second intervals. The end point was taken when the tube could be held horizontally without slipping at the blood-air interface. The times for the four tubes were averaged. The normal range of coagulation time when this technique is used is from five to eleven minutes.

Prothrombin Consumption Test

For the prothrombin consumption test the two-stage method of Merskey (1950*b*) was used. Fibrinogen supplied by Dr. A. Kekwick, of the Lister Institute, London, was used in a concentration of 150 to 200 milligrammes per 100 millilitres. The prothrombin consumption index was calculated as the ratio of the plasma clotting time to the one-hour serum clotting time recorded as a percentage. The prothrombin consumption index in a large series of normal blood specimens has ranged from 0 to 40% (mostly 0 to 20%).

Thrombin-Generation Test

The thrombin-generation test was carried out by the method of Pitney and Dacie (1953), with the following modifications. Venous blood was delivered from a siliconized syringe into a 1 : 10 volume of 3·8% sodium citrate solution in a chilled siliconized centrifuge tube. The blood was kept at 4° C. until tested (usually thirty minutes to one hour after collection). By this time the red cells had usually sedimented sufficiently, so that enough platelet-rich plasma could be pipetted off for the test without the need for centrifugation. The test was carried out in unsiliconized three inches by half an inch tubes.

Thromboplastin-Generation Test

The thromboplastin-generation test was carried out in accordance with the technique of Biggs and Douglas (1953). In some of the tests, a platelet substitute prepared from brain extract (Bell and Alton, 1954) was used instead of a washed platelet suspension. In four patients with very mild hæmophilia, this test gave equivocal results when carried out in the usual manner. In these instances, the test was made more sensitive by using the patient's and the normal aluminium-hydroxide treated ($Al(OH_3)$-treated) plasma at a dilution of 1 : 20 in veronal buffer (Owren, 1949) instead of the recommended dilution of 1 : 5 in saline. The factor-V content of the thromboplastin-generating mixture is not optimal when these high dilutions of plasma are tested. Additional factor V was therefore supplied by adding an equal volume of a 1 : 5 dilution of $Al(OH_3)$-treated plasma from a patient with severe hæmophilia. The AHG content of such plasma is negligible.

Assay of Plasma AHG Concentration

The method of assay of plasma AHG concentration (Pitney, 1956*a*) is based on the thromboplastin-generation test. The AHG content of test plasma is compared to that of a standard normal plasma. A series of dilutions from 1 : 20 to 1 : 2000 of normal $Al(OH_3)$-treated plasma are each incubated with a mixture consisting of a dilution of normal serum, a preparation containing factor V, a washed platelet suspension and calcium chloride solution. The amount of thromboplastin generated in each mixture is measured by subsampling at a fixed time from the incubation mixture together with excess calcium chloride solution into normal high-spun plasma. The clotting times of the substrate plasma are related to the AHG content of the $Al(OH_3)$-treated plasma dilutions. A standard dilution curve may be prepared by plotting substrate clotting times against the respective plasma dilution. Three dilutions of $Al(OH_3)$-treated

test plasma are used to replace the normal $Al(OH_3)$-treated plasma dilutions in the incubation mixtures and substrate plasma clotting times recorded. From reference to the standard dilution curve, the AHG content of each test plasma dilution can be calculated as a percentage of the normal.

The range of AHG concentrations in a series of normal specimens of plasma has been found to be from 50% to 220% of the standard normal plasma. Because high dilutions of normal and test plasma are compared in the assay procedure, AHG deficiency can be demonstrated when the thromboplastin-generation test, as ordinarily performed, gives a normal result.

Clinical Features

Age and Incidence

The age of the 19 patients when first diagnosed as suffering from hæmophilia ranged from nine to sixty-seven years, with an average age of thirty-six years; 15 were aged twenty-one years or over. Concurrently with this investigation, 46 patients suffering from severe hæmophilia, all with a prolonged whole-blood coagulation time, were seen. The incidence of the mild form of the disease in the total series of patients with hæmophilia was therefore 19 out of 65 (29%). In contrast to the large number of adults seen in the mild group, all of those in the severe group had been diagnosed as suffering from some form of hæmorrhagic disorder during the first few years of life.

Family History

Seventeen families are represented in the series of mild hæmophiliacs. Two of the 19 patients were brothers, two others were first cousins (their mothers were sisters). The incidence of positive family histories is more correctly calculated on the basis of family representation than on individual cases seen. Eight of the 17 families (47%) had a history of abnormal bleeding in one or more members other than the one studied. As far as could be determined, the severity of symptoms seemed to be about the same in affected members of the same family. Forty-one families are represented by the 46 patients seen concurrently with severe hæmophilia. In three of these the family history was not reliable. Of the remaining 38 families, there was a history of abnormal bleeding in other than the member studied in 24 (63%). If the whole group of hæmophiliacs is considered collectively, there was a positive family history in 32 out of 55 families studied, an incidence of 58%.

Clinical History

1. *Excessive Bleeding Following Tooth Extraction.*—This was by far the commonest symptom, and a history of abnormal bleeding after tooth extraction was obtained in 18 of the 19 patients. The one patient who did not give such a history was the youngest, a boy, aged nine years, who had lost his primary dentition without incident, but to date had had no permanent teeth removed. The character of the bleeding varied: in some patients, tooth extraction had been followed by a steady ooze of blood from the gums for from several days to several weeks; in other patients, bleeding ceased within the normal time, only to restart several days later and then be difficult to control. In several patients bleeding after tooth extraction was almost the only symptom of which the patient complained.

Case 3.—A.McD., aged thirty-one years, gave a history of excessive hæmorrhage after a tooth was knocked out when a child. He required transfusion at this time. When aged eighteen years he underwent appendicectomy without abnormal bleeding. In the same year he had four teeth removed when in the Army. He bled on and off for six weeks and required transfusion. When he was aged twenty-one years, a lesion was removed from his lip, which resulted in excessive hæmorrhage, and again he was transfused. Apart from these incidents he had no disability, led an active life and played several types of sport. There was no family history of abnormal bleeding.

2. *Excessive Bleeding Following Surgical Procedures.*—Several patients were referred for investigation because of abnormal bleeding following surgery. In all, there was a previous history of excessive hæmorrhage following tooth extraction, when this had been performed.

Case 13.—M.W., aged twenty-one years, suffered from pulmonary tuberculosis and had had a recent right-sided plombage. He bled into the chest for three days and was transfused with five pints of blood before the bleeding stopped. As a child he bled for two weeks from a broken tooth stump and required transfusion. He had bled for a week after tonsillectomy. Four years ago he bled for a week after tooth extraction. The family history was negative.

3. *Gastro-Intestinal Hæmorrhage.* — Four patients gave a history of gastro-intestinal hæmorrhage. In three, repeated hæmatemeses and/or melæna were the main symptoms for which the patients were referred for examination. In two of these, an organic lesion was found in the alimentary tract, which was presumably the source of the bleeding.

Case 17.—A.R., aged fifty-eight years, had always bled abnormally after tooth extractions, and the sockets were usually plugged. Otherwise he had no

symptoms until three years previously. Since then he had had repeated attacks of melæna and needed transfusion once. A duodenal ulcer was visualized radiologically. Because of the suggestive history of abnormal bleeding following tooth extraction, he was referred for examination before operation was undertaken. A brother also suffered from excessive bleeding after tooth extraction.

4. *Hæmarthroses.*—Only three patients in this series had suffered from hæmarthroses, and none had any serious resulting disability. In Case 1 the patient had had a swollen painful elbow on one occasion, which had subsided with no residual stiffness. In Case 2 the patient had some disability of the left ankle following repeated episodes of pain and swelling, and the right elbow had also given some trouble. In Case 11 the patient had been suffering from "osteoarthritis" of the right ankle and knee since the age of forty years. Many of the other patients led quite strenuous lives without joint disability. Most had served in the Armed Forces without symptoms of any kind. One was a prison warder and a judo instructor. Another was a fast bowler in the school cricket team. Another had practised cross-country running as a hobby for several years.

TABLE I

Summary of Clinical Findings in Nineteen Patients with Mild Hæmophilia[1]

Case Number	Initials	Age (Years)	Family History	Excessive Bleeding After Tooth Extraction	Gastro-Intestinal Hæmorrhage	Hæmarthroses	History of Blood Transfusion	Other Data
1	E.F.	29	–	+	+	Swollen elbow once. No disability	+	Gastric ulcer present.
2	R.D.	36	+	+	–	Left ankle and right elbow	–	Excessive bleeding from cuts and abrasions
3	A.McD.	31	–	+	–	Nil	+	Appendicectomy without incident. Excessive bleeding after surgery to lip
4	C.D.	43	–	+	–	Nil	+	Excessive bleeding from cuts
5	C.B.[2]	15	+	+	–	Nil	–	Excessive bleeding from cuts. Frequent epistaxes
6	R.H.[2]	14	+	+	–	Nil	+	Excessive bruising
7	A.C.	60	–	+	+	Nil	+	Repeated attacks of melæna without demonstrable lesion
8	T.D.	43	+	+	–	Nil	–	Operation on knee after football injury without incident
9	A.E.	31	+	+	–	Nil	–	No other symptoms
10	F.S.	46	–	+	–	Nil	–	Bled excessively after surgery to pilonidal sinus. Blew off three fingers in shotgun accident without excessive bleeding
11	A.T.	56	+	+	–	"Osteoarthritis" of right ankle and right knee	+	Hæmaturia once
12	W.T.	43	–	+	–	Nil	+	Bled excessively after minor surgery to rectum. Bled excessively after tonsillectomy when a young man
13	M.W.	21	–	+	–	Nil	+	Excessive bleeding after tonsillectomy when a child. Recently bled excessively after plombage for pulmonary tuberculosis
14	F.M.	29	–	+	–	Nil	+	Excessive bleeding after tonsillectomy
15	B.L.	15	+	+	–	Nil	+	Frequent epistaxes
16	D.C.	9	–	No permanent teeth extracted	+	Nil	+	Excessive bleeding after tonsillectomy. Melæna on one occasion
17	A.R.[3]	58	+	+	+	Nil	+	Duodenal ulcer present
18	F.R.[3]	67	+	+	–	Nil	–	No other symptoms
19	D.T.	35	+	+	–	Nil	–	Lacerated scalp bled excessively when a child

[1] "+" = a positive finding; "–" = a negative finding.
[2] First cousins.
[3] Brothers.

5. *History of Blood Transfusions.*—A history of having required blood transfusion because of abnormal bleeding provides an indication of the severity of the hæmorrhagic episode. Twelve of the 19 patients had been transfused because of excessive bleeding following teeth extraction, tonsillectomy or other surgery or gastro-intestinal bleeding.

The clinical features are summarized in Table I.

Laboratory Findings

The laboratory findings are summarized in Table II. Case numbers refer to the same patients as in Table I.

Whole-Blood Coagulation Time

The whole-blood coagulation time was normal in all patients, values ranging from seven and a quarter to eleven minutes. The tendency was for the coagulation times to be nearer the upper than the lower limit of normal. Thus 10 patients gave values of from nine to eleven minutes. Estimations of coagulation time were not performed in silicone tubes as is done by some workers in an attempt to increase the sensitivity of the test.

Prothrombin Consumption Index

If the normal range of 0 to 40% is accepted for the prothrombin consumption test, prothrombin consumption was normal in 13 of the 19 patients. If a large series of normal subjects are tested, most indices will fall between 0 and 20%, and only an occasional value be obtained as high as 40%. If stricter limits of normality of 0 to 20% are used, only six patients gave a normal result with this test. The practice has been to view values of 20% to 40% with suspicion as indicating the need

Table II

Summary of Laboratory Findings in Nineteen Patients with Mild Hæmophilia

Case Number[1]	Whole Blood Coagulation Time (Minutes)	Prothrombin Consumption Index (*per Centum*)	Thrombin Generation Test[2]	Thromboplastin Generation Test[3] [6]	Plasma AHG Concentration[5] (*per Centum*)
Normal range	5–11	0–40	Normal	One or more 10 or less[4]	50–220
1	10½	30	—	80, 60, 60, 35, 21, 23	—
2	8½	27	—	42, 30, 19, 16, 17, 21	6
3	7½	17	—	60, 22, 15, 15, 14, 14	25
4	8½	33	Abnormal	60, 40, 19, 16, 14, 13½	10
5	7½	49	Normal	65, 45, 21, 11½, 11½, 13	19
6	9½	37	Normal	60, 37, 13, 10½, 10½, 12	15
7	9½	34	Normal	35, 16, 9, 8½, 9, —	16
8	8	95	Abnormal	60, 28, 17, 15, 13½, 12	7½
9	8½	30	Normal	60, 35, 24, 20, 17, —	7½
10	9	60	Normal	20, 12, 13, 12, 11, 11	4
11	11	7	Abnormal	28, 19, 16½, 15½, 15½, 15½	3
12	10½	24	Normal	37, 16½, 13½, 12½, 13, 12½	15
13	9½	66	Normal	36, 27, 15, 13½, 13½, 12	14
14	8	85	Abnormal	39, 31, 19½, 16, 16, 15	3
15	10½	100	Normal	41, 23, 13, 13, 16, 17	—
16	10	10	Normal	33, 13, 8, 9, 9[6]	27
17	8	Less than 5	Normal	11½, 10, 10, 8½, 8½, 8½	31
18	7½	Less than 5	—	27, 12, 12, 10, 9, 10	38
19	9½	15	Abnormal	80, 60, 60, 32, 21, 15, 16	9

[1] Case numbers refer to Table I.
[2] "—" indicates that the test was not performed.
[3] The series of six figures refer to the clotting times in seconds of substrate plasma when subsamples were made at one-minute intervals from an incubation mixture containing the patient's $Al(OH_3)$-treated plasma diluted 1 : 5, normal serum diluted 1 : 10, a washed platelet suspension (Cases 1–17) and calcium chloride. In Cases 18 and 19, a platelet substitute prepared from brain extract was used instead of a washed platelet suspension.
[4] Normal control figures always reach 10 seconds or less within 6 minutes.
[5] The result of the test was abnormal when the patient's plasma and serum were tested together.
[6] In Cases 7, 16, 17, 18 where the result of the thromboplastin-generation test was normal, further testing with more dilute plasma samples revealed an abnormality.

for further tests, even though, when considered alone, such a result may have little diagnostic value. Used in this way, the test had definite value.

Thrombin-Generation Test

The thrombin-generation test was performed on 15 patients. A normal result was obtained in 10. Generally it was of less value in indicating an abnormal clotting mechanism than the prothrombin consumption test. However, both tests did not necessarily measure the same effect, since in three patients (Cases 4, 11, 19) the thrombin-generation test gave an abnormal result when the result of the prothrombin consumption test was normal. Modifications of the test to increase sensitivity (Fantl and Sawers, 1954) were not used in this investigation.

Thromboplastin-Generation Test

The thromboplastin-generation test was by far the most sensitive of the routine tests employed. In 15 of the 19 patients, a clear abnormality was detected when the test was carried out in the usual manner. In another patient (Case 16) the test gave normal values when the patient's $Al(OH_3)$-treated plasma at the usual dilution of 1 : 5 was tested with normal serum. When the patient's plasma and serum were tested together, prolonged clotting times were observed. Further investigation showed that this patient also suffered from a mild deficiency of a serum clotting factor. In this patient and also in three others (Cases 7, 17, 18) whose plasma tested in the usual dilution gave a normal result, further testing of more dilute plasma samples revealed an abnormality. In every patient, therefore, the thromboplastin-generation test revealed evidence of AHG deficiency, although in four patients modifications to increase the sensitivity of the test were necessary.

AHG Plasma Concentration

In 17 patients in whom plasma AHG concentrations were assayed, values ranging from 3% to 38% were obtained. As stated previously, the normal range has been found to be from 50% to 220% of that of the standard normal plasma. The patient with a concentration of 38% (Case 18) was the mildest bleeder in this series, and could be considered a subclinical hæmophiliac. He was tested only because his brother (Case 17) was under investigation, and it was desired to carry out a family study.

CASE 18.—F.R., aged sixty-seven years, gave a history of excessive bleeding following tooth extraction, but no other hæmorrhagic tendency. He had bled for a week after a tooth was removed at the age of fourteen years. Two years previously, a tooth had been removed and bleeding had ceased after twenty-four hours, but restarted a week later. Recently he had had seven teeth out at the same time. He had bled for twenty-four hours, and then the gums were sutured. Bleeding ceased for two weeks, when further hæmorrhage necessitated resuturing.

In five patients plasma AHG concentrations were determined on more than one occasion. The results are shown in Table III, and indicate that each patient maintained the same order of concentration. The coefficient of variation between three observations on the same plasma with this assay method has been calculated to be from 11% to 22% (Pitney, 1956*a*), and the variations in concentration noted could be due to the experimental error of the assay rather than to fluctuations in plasma AHG content.

TABLE III

Results of Three Observations of Plasma AHG Concentrations in Five Patients with Mild Hæmophilia

Case Number	Plasma AHG Concentration (*per Centum*) (Normal Range 50 to 220).		
	1	2	3
4	10	6	8½
7	16	24	—
9	7½	7	—
16	20	27	—
17	31	32	23

DISCUSSION

Most of the patients in this series did not have their condition diagnosed until adult life, even though there was a history of abnormal bleeding after tooth extraction dating back to childhood or early adolescence. This emphasizes the mildness of their symptoms, and also indicates that a mild hæmorrhagic disorder detected for the first time even in an elderly male may be due to a previously undiagnosed mild hæmophilia.

In nine of the 17 families represented (53%), there was no evidence of familial bleeding. A negative family history is not unusual even in severe hæmophilia. Merskey (1950*a*) could find no evidence of inheritance in 28 out of 72 hæmophiliacs (39%) examined by him, and in the series of severe hæmophiliacs examined concurrently with those in this mild series, there was no history of familial bleeding in 37%.

The severity of hæmophilia in affected members of the same family tends to be of

similar grade. The patients with mild hæmophilia who had affected relatives all stated that the severity of the disease within the family was of a similar type. In Cases 5 and 6 the patients, who were first cousins, had approximately the same severity of disease clinically; the plasma AHG concentrations were 19% and 15% respectively. In Case 17 the condition would probably never have been diagnosed if the patient had not suffered from a duodenal ulcer. His plasma AHG concentration was 31%. His brother (Case 18) presented for examination only because he was requested to do so. His symptoms were very mild, and his plasma AHG concentration 38%. It would be expected that a series of mild hæmophiliacs would show a lower percentage of positive family histories than a comparable series of severe hæmophiliacs because in the mild group the condition might remain undiagnosed in affected relatives.

The most constant and often the only symptom in this group of mild hæmophiliacs was excessive bleeding after tooth extraction. In most patients excessive bleeding occurred each time teeth were removed, even though the dentist was warned that this was likely to occur and presumably performed the extractions carefully. Excessive bleeding after tooth extraction is thus an important symptom to elicit in taking the history of a suspected mild "bleeder". Conversely, if a patient has had teeth removed on more than one occasion without excessive bleeding, it would seem unlikely that he is a hæmophiliac.

Patients have varied opinions as to what constitutes abnormal bleeding after teeth extraction. Some patients claim that they bleed excessively if they lose a volume of blood considered to be more than normal, even though bleeding stops in the normal time. This is not typical of hæmophilic bleeding. The briskness of a hæmorrhage depends upon the number and size of the vessels lacerated during the extraction, and is not influenced very much by the state of the hæmostatic mechanism. The patients with mild hæmophilia mostly complained of a slow ooze from the sockets which continued for several days or even weeks. Initially blood loss was no greater than with a normal person, but bleeding did not cease in the normal time. It is difficult to be dogmatic as to how long normal individuals should bleed after tooth extraction. Macfarlane and Biggs (1955) believe that most normal people have stopped bleeding after twenty-four hours, and they state that bleeding for forty-eight hours after tooth extraction or bleeding that requires a blood transfusion probably indicates a derangement of the blood-clotting mechanism.

Bleeding may continue for a surprisingly long time even in mild hæmophilia after tooth extraction, particularly if several teeth are removed at the same time. In Case 4 the patient, who led a normal life with virtually no disability, had several teeth removed by a dentist while serving in the Royal Navy, and spent nine weeks in the sick bay having repeated transfusions. Tooth extraction is probably as severe a test of the hæmostatic mechanism as some major surgery. Thus in Case 3 the patient, who bled for six weeks and required blood transfusions after having four teeth removed, underwent an appendicectomy the same year without incident. It should be remembered, however, that patients may have an increased liability to bleed at some times rather than at others. It is well known that severe hæmophiliacs have good and bad periods, and the occasional patient with mild hæmophilia will experience no trouble with one tooth extraction, and bleed excessively at other times.

The case histories of nearly all these patients can be summarized as consisting of excessive bleeding only when the hæmostatic mechanism was put under stress. Two of the three patients who were referred because of repeated gastro-intestinal bleeding suffered from ulceration of the gastro-intestinal tract, and it is reasonable to suppose that the erosion of a vessel in an ulcer which might stop bleeding in a short time in a patient with normal clotting function would result in persistent bleeding in these patients. Hæmarthrosis, although common in severe hæmophilia, was not an important symptom in these case histories.

It has been recognized for some time that the whole-blood coagulation time is a very insensitive index of clotting function. Relatively small volumes of plasma when transfused to patients with severe hæmophilia will result in restoration of the clotting time to normal (Alexander and Landwehr, 1948). However, such patients may continue to bleed, indicating that the hæmostatic mechanism is still deranged. A normal blood coagulation time therefore has little value in the exclusion of a possible hæmostatic defect. Patients with hæmophilia who have prolonged coagulation times usually have a severe grade of AHG deficiency, and there is little doubt from the clinical histories that such patients are "bleeders".

Some workers believe that the coagulation time test can be made more sensitive by carrying out the technique with siliconized tubes to delay clotting. Advantages of such a procedure are doubtful, since the normal range which is used for comparison is very much widened as well as being delayed, and it becomes more difficult to determine whether an observed result is normal or not. Fortunately the more sensitive tests of clotting function that are now available reduce the significance of the coagulation time as a diagnostic procedure. From a comparison of the results of the whole-blood coagulation time and assay of plasma AHG concentration, it seems that about 2% AHG is necessary to give a normal coagulation time (Pitney, 1956*b*).

Like the coagulation time, the prothrombin consumption test is non-specific. The test gives an indication of the amount of prothrombin which is not converted to thrombin during clotting, and thus indirectly of the efficiency of thromboplastin production. Platelet deficiency as well as deficiencies of thromboplastin-precursor substances may produce an abnormal result with this test. Although a more sensitive index of clotting function than the whole-blood coagulation time, the test gave a normal result with several of the patients in the present series. It is a difficult test to standardize ; and if the same patient is tested on several occasions, a wide range of values is possible. Some of the patients who gave abnormal values with this test produced a normal result when tested on another occasion. The normal range is so wide and its limits still so uncertain that it is not surprising that considerable overlap occurs between normal and abnormal with this test. It is probable that about 5% AHG is necessary to produce normal prothrombin consumption. This is, however, only a generalization because the result of the test was normal in Case 11 (with a plasma AHG concentration of 3%) and abnormal in cases 5, 8 and 13, in all of which AHG concentrations were greater than 5%.

The thrombin-generation test as originally described has little value in the diagnosis of mild hæmophilia. In three patients (Cases 4, 11, 19) the test gave information that the prothrombin consumption test did not. Usually, however, it was less sensitive than the latter test. A more sensitive test involving use of the same principle has been described (Fantl and Sawers, 1954).

The thromboplastin-generation test proved to be easily the most sensitive test in the diagnosis of these cases. In most the test was clearly abnormal when performed in the usual manner. In a few patients it was necessary to increase the sensitivity of the test by using higher plasma dilutions than originally described. All patients showed a clear abnormality when the plasma was tested at a 1 : 20 dilution. However, it is important to add a source of factor V to the generating mixture when this dilution is used.

From the results given by multiple testing of these patients, it is recommended that the thromboplastin-generation test be carried out on any male patient who gives a history of abnormal bleeding that could be consistent with the diagnosis of mild hæmophilia. The other tests described here are so insensitive that normal results obtained with them are liable to be misleading.

Brinkhous *et alii* (1954) suggest that the inherited gene of hæmophilia exists in the population as a probably continuous series of isoalleles, each one of which is responsible for a characteristic level of plasma AHG activity. In this group of patients, all grades of deficiency between 38% and 3% were found, and on the basis of AHG assays, the mild hæmophiliacs seemed to merge imperceptibly into the severer grades, who showed either none or only traces of AHG in their plasma. Brinkhous *et alii* (1954) also believe that, since the plasma AHG concentration is genetically determined, it is relatively constant in any one individual. This seems to be substantiated by the observations recorded in Table III, in which AHG plasma assays were performed on more than one occasion on five mild hæmophiliacs.

Plasma AHG assay procedures have enabled a better understanding of the principles of treatment in a hæmophiliac who is bleeding as a result of his disease, and also make possible more satisfactory laboratory control of therapy. If the aim of therapy is to correct the hæmostatic defect, an attempt should be made to raise the plasma AHG level to 30% (Macfarlane *et alii*, 1954). This entails the transfusion of a large volume of plasma, which should be fresh, since AHG activity rapidly diminishes in stored plasma (Pitney, 1956*a*).

An illustration of the control of therapy with plasma AHG estimations is provided by Case 19. When seen the patient had been bleeding from tooth sockets for ten days. His plasma AHG assay was 9%. To raise this to 30% it was estimated that fresh plasma equal to at least one-fifth of his plasma volume would have to be rapidly transfused. One litre of four-hour-old plasma was given over a one-hour period. A plasma sample withdrawn immediately

after the transfusion contained 30% AHG. A sample four hours later contained 40% AHG, while a further sample withdrawn the next morning, sixteen hours after the transfusion, still contained 23% AHG. Thus the patient was kept with a fairly normal hæmostatic mechanism for a period of sixteen hours. Bleeding ceased soon after the plasma was given, and did not recur.

This patient was the only mild hæmophiliac in whom it was possible to administer plasma and study plasma AHG concentrations. The results are of interest because all the transfused AHG could be accounted for in the patient's plasma. This is not the usual experience in severe hæmophilia, where it is estimated that two and a half times the calculated AHG may have to be given to raise the plasma concentration to the desired level (R. G. Macfarlane, personal communication). It is possible that undetected inhibitors present in the blood of some hæmophiliacs may account for the difference.

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BLOOD GROUPS AND DISEASE: PULMONARY TUBERCULOSIS[1]

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SUMMARY

The A B O, M N S and Rh blood groups have been determined on 470 patients suffering from active pulmonary tuberculosis. The distribution is similar to that found in the random Australian population except that there are fewer group AB subjects amongst the patients. This finding is probably not significant.

IT is now well established that the great majority of patients with pulmonary tuberculosis develop the disease after contact with an "open" case. Undoubtedly dissemination of the causative organism, *Mycobacterium tuberculosis*, is the important factor in this as in other infectious diseases. However, there is evidence that the resistance of the exposed individual also plays a part and that environmental factors may lower this resistance. For example, the general malnutrition which occurred in some European countries after World War II produced a large increase in the incidence of active cases, and the disease is much more prevalent in undernourished Asian countries than in the Western world.

Although it has been suggested that genetic factors in man may determine the susceptibility or resistance to the disease of an individual subject, no proof of this contention has ever been produced. Investigations are difficult because it is rarely possible to eliminate environmental factors. The most satisfactory approach has perhaps been the fate of the other twin when the sufferer happens to be a twin. Even this is open to the objection that identical twins are nearly always more closely associated than are non-identical twins (Report of the Medical Research Council, 1954).

Strong support for a genetic factor would be obtained if it could be shown that the blood group distribution of a series of patients with active tuberculosis differed from the distribution found in the random population. For this reason the blood groups of 470 patients were determined, and the results are reported in this paper.

METHODS AND MATERIALS

Subjects included in this survey either were hospital patients in the Bodington Red Cross Hospital, Wentworth Falls, or were being investigated at the Anti-Tuberculosis Association Clinic, Sydney. None was accepted unless radiographic diagnosis of pulmonary tuberculosis had been supported by isolation and identification of the causative organism. Dr. N. R. Godby arranged for the collection and forwarding of 183 blood samples from the Bodington Hospital, whilst the remaining 287 samples were collected at the Anti-Tuberculosis Association Clinic by Mr. J. Bell and by arrangement with Dr. M. Glick.

Blood was collected aseptically from the cubital veins of the subjects, and approximately two millilitres were allowed to clot in sterile three inches by three-eights of an inch test tubes. Red cells from the clots were suspended in physiological saline solution and washed twice with fresh saline before use. The blood groups were determined by the methods described by Mollison *et alii* (1952), and the gene frequencies were calculated by the methods of Race and Sanger (1952). The samples were always tested within five days of collection, and on all

[1] Received on April 12, 1956.
[2] Serologist.
[3] Director.

occasions the antisera used were tested against red cells containing and red cells lacking the corresponding antigens.

RESULTS

An analysis of the A B O groups is shown in Table I. There is close agreement between the observed numbers and those expected on the basis of the calculated gene frequencies (χ^2=1·59 for one degree of freedom), indicating that the tested series is homogeneous within itself. The distribution of the groups in a random series of 1123 Australian subjects, as determined by Simmons *et alii* (1951), is also shown in Table I. Unfortunately the group AB subjects in this random series were not divided according to the subgroups of A. χ^2 has been calculated to compare the distribution in the two series, and a significant value for χ^2 (15·71 for four degrees of freedom; *P* less than 0·01) was obtained. The greatest contribution to the χ^2 value is in respect of the deficiency of the AB subjects amongst the tuberculosis patients. Only eight group AB subjects were detected, compared with an expected 19·18 as calculated from the two populations combined.

TABLE I

The A B O Groups

Group	Subjects with Tuberculosis			Observed in Random Australian Population
	Observed Absolute	Observed Frequency	Expected Absolute	
O	231	0·4915	228·33	500
A_1	146	0·3106	144·32	333
A_2	45	0·0957	44·50	95
B	40	0·0851	39·51	138
A_1B	6	0·0128	9·81	57
A_2B	2	0·0043	3·53	
Total ..	470	1·0000	470·00	1123

Gene frequencies
O =0·6970
A_1=0·1802
A_2=0·0649
B =0·0579

TABLE II

The M N S Groups

Group	Subjects with Tuberculosis			Observed in Random Australian Population
	Observed Absolute	Observed Frequency	Expected Absolute	
MMS	87	0·1851	92·01	30
MsMs	37	0·0787	39·36	9
MNS	127	0·2702	120·60	40
MsNs	122	0·2596	113·63	27
NNS	21	0·0447	22·40	13
NsNs	76	0·1617	82·00	21
Total ..	470	1·0000	470·00	140

Gene frequencies
MS=0·2393
Ms =0·2894
NS=0·0536
Ns =0·4177

The M N S groups are shown in Table II. Again the expected and observed numbers approximate. The distribution of the phenotypes in the random Australian population (Walsh and Montgomery, 1947) has been compared with that in the series, but the differences were not significant (χ^2=7·43 for five degrees of freedom; *P* lies between 0·10 and 0·20).

TABLE III

The Rh Groups

Reactions with Antisera C c D E	Most Common Genotype	Subjects with Tuberculosis			Observed in Random Australian Population
		Observed Absolute	Observed Frequency	Expected Absolute	
+ + + −	CDe /cde	155	0·3298	168·02	105
+ − + −	CDe /CDe	88	0·1872	88·00	54
− + + +	cDE /cde	77	0·1638	67·01	33
+ + + +	CDe /cDE	62	0·1319	62·19	45
− + − −	cde /cde	74	0·1574	74·00	52
− + + −	cDe /cde	7	0·0149	6·98	5
+ + − −	Cde /cde	4	0·0085	0·82	3
− + − +	cdE /cde	2	0·0043	1·99	3
+ − + +	CDE/CDe	1	0·0021	0·98	0
Total ..	—	470	0·9999	469·99	300

Gene frequencies
CDe (R_1) =0·4305
cDE (R_2) =0·1445
cDe (R_0) =0·0183
CDE (R_z) =0·0024
cde (R^*) =0·0053

The Rh groups are shown in Table III. The phenotype distribution between the two series does not differ significantly (χ^2=4·97 for five degrees of freedom; *P* lies between 0·3 and 0·5). For this comparison the last four phenotypes were combined to give a total of 14 amongst the tuberculosis patients and 11 in the control series, as determined by Simmons and Graydon (1950).

DISCUSSION

The only difference between the blood groups of the Australian population and those of the patients with pulmonary tuberculosis is a deficiency of group AB subjects in the latter series. More weight would be attached to this finding if it concerned a phenotype in which not all the subjects were heterozygotes, and if the number of subjects involved in the pheno-

type were greater. In spite of the statistical test, it would seem likely that the observed difference is due to chance.

The absence of a definite association between the occurrence of a disease and the blood groups does not invalidate the hypothesis that the particular disease or the susceptibility to it is inherited. It is possible that blood group systems other than those investigated may show some positive association with the occurrence of the disease. There is no theoretical reason why any one blood group system should be important in this regard ; but it is of interest and perhaps of significance that to date only the A B O groups have been involved in positive association with such diseases as carcinoma of the stomach (Aird *et alii*, 1953 ; Billington, 1956), peptic ulceration (Aird *et alii*, 1954) and fatal bronchopneumonia in infants (Struthers, 1951).

Further possibilities in pulmonary tuberculosis are, firstly, that the gene or genes determining susceptibility to the microorganism may not be closely linked to any of the blood group loci, and, secondly, that these genes may be situated on different chromosomes.

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A NOTE ON A B O BLOOD GROUP DISTRIBUTION IN CARCINOMA OF THE ŒSOPHAGUS AND CARDIA[1]

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SUMMARY

In 119 cases of squamous carcinoma of the œsophagus the A B O blood group distribution has not shown significant difference from that of a control population.

The A B O blood group distribution in 86 cases of carcinoma of the cardia of the stomach appears to show a significant difference from that of a control population, the incidence of group A being 19·7% above the expected value.

IN a previous communication it was suggested that a relationship existed between the localization of lesions in the stomach and the A B O blood groups (Billington, 1956). It was noted that for both carcinoma and chronic gastric ulcer, prepyloric lesions were significantly associated with blood group A and non-prepyloric lesions were associated with group O. It was also suggested that further blood group localization associations might be found in the non-prepyloric part of the stomach.

In the knowledge that cardiac glands resemble those in the prepyloric region and differ from those in the body and fundus of the stomach (Maximow and Bloom, 1952) and that the secretory pattern of gastric glandular mucoprotein differs according to whether the gastric carcinoma arises in the body and fundus on one hand and the cardia or prepyloric regions on the other (Wolf *et alii*, 1953), this investigation was undertaken to determine whether carcinoma arising from the cardia of the stomach is also associated with blood group A.

[1] Received on June 27, 1956.

[2] Working on a part-time research grant from The Royal Australasian College of Physicians.

MATERIAL

The records of public in-patients from four Sydney teaching hospitals were analysed for the period 1947 to 1954. Data from immigrants were not allowed. It was possible to record the A B O blood group of 86 subjects with proven carcinoma of the cardia and of 119 with carcinoma of the œsophagus.

The following criteria were employed:

Carcinoma of the Œsophagus: Cases were admitted when there was macroscopic evidence at œsophagoscopy, operation for resection or autopsy together with microscopic evidence of squamous carcinoma of the œsophagus.

Carcinoma of the Cardia: Cases were admitted when there was macroscopic evidence at resection or autopsy, with microscopic confirmation of adenocarcinoma involving the cardio-œsophageal junction, or involving the

TABLE I

A B O Blood Group Distribution in New South Wales Blood Donors and Patients with Carcinoma of the Œsophagus and Cardia

Population	Number	Group A	Group B	Group O	Group AB	Comparison with Controls A : O : AB+B Ratio	
						χ^2 for Heterogeneity (Degree of Freedom = 2)	Probability
New South Wales blood donors (Walsh, 1947)	30,000	11,514 (38·38%)	2,912 (9·70%)	14,672 (48·91%)	902 (3·01%)	—	—
Patients with carcinoma of the œsophagus	119	54 (45·4%)	12 (10·1%)	50 (42·0%)	3 (2·5%)	2·67	>0·2
Patients with carcinoma of the cardia	86	50 (58·1%)	6 (7·0%)	24 (27·9%)	6 (7·0%)	16·65	<0·001

stomach to a distance not exceeding three centimetres from the cardio-œsophageal junction.

Controls: The figures of Walsh (1947) for the A B O blood group distribution of 30,000 consecutive donors to the New South Wales Red Cross Blood Transfusion Service, Sydney, were used.

Results

The results are shown in Table I. If we take groups B and AB together, there is no significant difference in the A B O blood group distribution in squamous carcinoma of the œsophagus when compared with the control blood donor population ($\chi^2=2\cdot67$ with two degrees of freedom; $P>0\cdot1$). In carcinoma of the cardia there appears to be a highly significant difference in the A B O blood group distribution when compared with the control population ($\chi^2=16\cdot65$ with two degrees of freedom; $P<0\cdot001$), the incidence of group A subjects being 19·7% above the expected value.

Discussion

Aird *et alii* (1954) have pointed out that in studies of this type two classes of controls can be used; the A B O blood group distribution of a large number of blood donors from the same area is likely to be unbiased, and the A B O blood group distribution of subjects suffering from a disease where there is no demonstrable difference in blood group frequency from a large number of donors can serve as a hospital control. In this series, from four hospitals, there is no significant difference in the A B O blood group distribution in subjects with squamous carcinoma of the œsophagus when compared with the blood donor controls. The numbers are too small for the figures from each hospital to be considered separately, but there is no significant difference in the ratio of squamous carcinoma of the œsophagus to carcinoma of the cardia from each hospital. It would appear, therefore, that within the small numbers collected, carcinoma of the cardia is significantly associated with blood group A.

It may be argued that a proportion of the cases included as carcinoma of the cardia may represent cases of adenocarcinoma arising from œsophageal mucous glands in the lower end of the œsophagus, although adenocarcinoma in the lower end of the œsophagus may also arise from aberrant gastric glands (Morson, 1954); it has been necessary, therefore, to demonstrate that at least in squamous œsophageal carcinoma there is no significant difference in A B O blood group distribution when compared with controls.

No apology is made for the smallness of the numbers included, as any one centre is unlikely at the present time to have a very much larger series conforming to these necessarily strict criteria; the purpose of this report is to stimulate interest elsewhere to confirm these findings, so that cumulative figures and controls may be interpreted with confidence.

Acknowledgements

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AUTOERYTHROCYTE SENSITIZATION WITH A CIRCULATING FIBRINOLYTIC FACTOR[1]

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SUMMARY

A woman, aged forty years, had suffered painful spontaneous bruising from the time of the menarche at the age of fourteen years. Prior to this and subsequently she had suffered a number of episodes of severe bleeding, usually two or three days after minor surgery or confinement. At the time of study she had suffered an intracranial hæmorrhage.

Autoerythrocyte sensitization and also a circulating fibrinolytic factor were demonstrated. This factor was thought to be associated with her red cells. Infusion of human serum albumin was associated with subjective and objective improvement.

A SYNDROME of painful bruising with autosensitization to red blood cells has been described by Gardner and Diamond (1955) following the investigation of four women who showed an abnormal response to bruising characterized by local pain, swelling and extension of bleeding into adjacent areas. Intradermal injection of the patient's own red cells produced the same abnormal response and led to the concept of autoerythrocyte sensitization.

This report concerns a woman with identical features and in addition a circulating fibrinolytic factor was demonstrated.

REPORT OF A CASE

The patient L.H. (GH 874), aged forty years, a housewife, is the youngest member of a family of three, and there is no family history of bleeding diseases. When six years old she broke her nose and mandible in a riding accident, but there was no excessive bleeding at this time. She had epistaxes as a child but no severe bruising. At the age of twelve years several teeth were extracted without excessive bleeding until three days later, when profuse hæmorrhage occurred for which she was admitted to hospital. Her menarche occurred at the age of fourteen years and was associated with menorrhagia, which forced her to bed with every menstrual period during her teenage years. She can recall the onset of painful spontaneous bruises at about this time. A tonsillectomy was performed when she was twenty years old without troublesome bleeding at the time of operation, but three days post-operatively she bled severely, and the tonsillar bed had to be sutured twice.

At twenty-one years of age she became pregnant and, after seven months' gestation, had a normal baby, but three days *post partum* a profuse hæmorrhage necessitated vaginal packing and anti-shock measures. A menstrual flow occurred for one to two days at monthly intervals throughout this and every subsequent pregnancy.

She had further teeth extracted, but they were removed singly, at intervals, and without serious bleeding. She had three further pregnancies when aged thirty-three, thirty-seven and thirty-nine years, all of which resulted in premature live babies, although the last two died shortly after birth. She had no bleeding complication with any of these confinements.

Three months prior to admission to hospital she developed severe frontal and occipital headache, became blind, was unable to move for several minutes and was left with a slight left hemiparesis. The headaches worsened, vomiting became distressing, and two days after the first episode she had impaired visual acuity in the left eye, and her left arm and leg were weak. Examination of the cerebro-spinal fluid revealed clear fluid under normal tension, arteriograms and ventriculograms were normal, but an electroencephalogram revealed a right-sided abnormality consistent with an intracerebral lesion. She improved very rapidly in hospital and had no residual neurological symptoms or signs, but she developed extensive painful bruises on the lower parts of the legs (Figure I) and she was seen in the Clinical Research Unit. Physical examination showed the presence of widespread bruising; her spleen was not palpable, and she was normotensive.

The results of laboratory investigations were as follows: the blood group was ORh-positive; the total red cell count was 4,260,000 per cubic millimetre; the hæmoglobin value was 13·1 grammes per 100 millilitres; the total white cell count was 6100 per cubic millimetre; the differential count showed neutrophile cells 3721 per cubic millimetre, lymphocytes 1891 per cubic millimetre, monocytes 244 per

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cubic millimetre and eosinophile cells 244 per cubic millimetre; the results of Wassermann and Kline precipitation tests were negative; the protein fractions of the patient's fresh plasma, determined by free boundary electrophoresis with the classical method in a Perkin-Elmer Tiselius apparatus, were normal (Figure II); direct and indirect Coombs reactions were negative; urine examination showed no abnormality.

FIGURE I

Extensive bilateral ecchymoses present at the time of commencing the study

Study of the patient's blood coagulation mechanisms revealed the presence of a circulating fibrinolytic factor, the properties of which are described later.

She was given 100 milligrammes of cortisone acetate daily for a period of eighteen days, during which time her bruising did not lessen but appeared to be

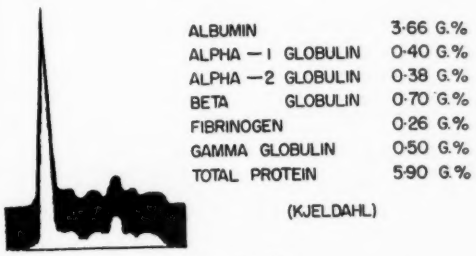

FIGURE II

The electrophoretic pattern of the patient's plasma

increased. An infusion of three grammes of human fibrinogen was given without apparent benefit, but three days later, while her bruising was particularly severe, infusion of 25 grammes of human albumin resulted in a more speedy resolution of her lesions. Two subsequent infusions of albumin during her stay in hospital were accompanied by similar improvement.

DEMONSTRATION OF AUTOERYTHROCYTE SENSITIZATION

Gardner and Diamond suggested the intradermal injection of the patient's own whole blood as a screening test for this condition.

A clean venepuncture was made in the antecubital fossa, and a "Tuberculin" syringe was filled with whole blood, a specimen being taken in another syringe for the determination of the hæmatocrit. A bleb was raised in the skin by the intradermal injection of 0·1 millilitre of whole blood through a fine needle. At the same time an intradermal injection was given to a control subject of the same blood group, the control subject's blood likewise being injected into the patient. The injected areas were inspected twenty-four hours after the injection, and the presence of induration was noted and the extent of the bruising measured. In the control and the patient the initial injection raised blebs measuring 0·5 centimetre by 0·5 centimetre, but the results at the end of the twenty-four hours were as shown in Table I and Figure III.

TABLE I

Blood Injected	Hæmatocrit	Bleb on Skin (Centimetres)	
		Patient	Control
Patient's blood ..	36%	6·3 by 5·0	1·5 by 1·3
Control's blood ..	44%	4·4 by 3·1	1·3 by 1·3

A curious feature of the cross experiment was the intense itching and pain resulting from the injection of the patient's own red cells, but not from the control cells, although the areas of induration were similar. The control was not disturbed by the test.

COAGULATION STUDIES (Table II)

All blood was carefully collected by a clean venepuncture into paraffin-lined syringes. Plasma was obtained by mixing the blood with one-tenth volume of Wintrobe's oxalate fluid and centrifuging the mixture at 3000 revolutions per minute for ten minutes.

After the removal of plasma, red cells were prepared from the packed cells by washing them three times with twice their volume of normal saline.

Platelet-rich plasma was prepared by collecting 10 cubic centimetres of whole blood through an 18-gauge siliconed needle into a siliconed and calibrated centrifuge tube containing one cubic centimetre of Wintrobe's

oxalate fluid and centrifuing at 15,000 revolutions per minute for ten minutes. The platelet-rich plasma was then removed with a siliconed Pasteur pipette.

A mixture of red and white cells was obtained by removing the buffy coat from the remaining

FIGURE III

Above: the patient's forearm twenty-four hours after the intradermal injection of 0·1 millilitre of whole blood; the superior bruise followed the injection of control blood, the inferior bruise followed the injection of the patient's own blood. Below: the control's forearm showing minimal bruising following the injections of the patient's and the control's whole blood

cells and washing them three times in twice their volume of normal saline.

The coagulation time was measured by the Lee and White method at 37° C. in tubes of internal diameter of 11 millimetres.

The plasma prothrombin time was estimated by Quick's one-stage method.

The serum prothrombin time (prothrombin consumption test) was measured by a modified Quick's method.

The bleeding time was obtained by Duke's method.

After incubating one millilitre of the patient's whole blood in each of two Lee and White tubes at 37° C. for one hour, clot retraction was present and the clot appeared normal; but one hour later it was slowly breaking up, and after twelve hours' incubation only a small attenuated clot remained suspended above a thick layer of red blood cells (Figure IV). This abnormal

TABLE II

Coagulation Studies

Test	Result
Coagulation time	6½ minutes
Bleeding time	1½ minutes
Prothrombin time:	
Patient	20 seconds
Normal control	19 seconds
Prothrombin consumption test:	
One hour	55 seconds
Normal	50 seconds

"falling out" of red cells has been observed in cases of hypofibrinogenæmia (Weiner *et alii*, 1950), of polycythæmia and of fibrinolysis (Reimann, 1941).

The patient's plasma fibrinogen content (Tiselius) was 260 milligrammes per 100 millilitres, which was slightly below the normal but hardly low enough to explain the dissolution

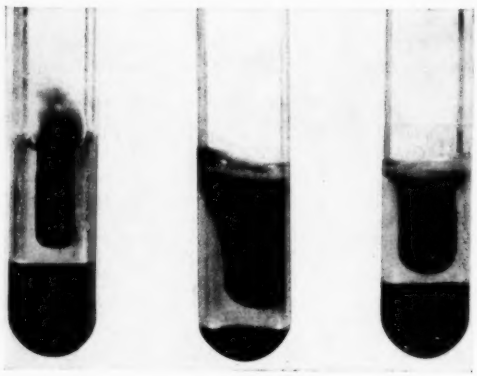

FIGURE IV

Each Lee and White coagulation tube contains one cubic centimetre of the patient's whole blood, which has been incubated at 37° C. for a minimum of forty-eight hours. The blood in the left-hand tube was collected prior to an albumin infusion and is representative of blood samples taken at various times during the patient's stay in hospital; there is a small attenuated clot with a large "pool" of red cells underneath. The middle tube was taken three hours after the patient was infused with 25 grammes of serum albumin, and shows an almost normal clot. The right-hand tube was collected twenty-four hours after the infusion; the clot still shows increased stability, but is returning to its original form

of her blood clot, since Cooperberg *et alii* (1955) have shown that a clot can remain intact with a fibrinogen concentration of 100 milligrammes per 100 millilitres. This con-

tention is supported experimentally by the failure of one millilitre of a fibrinogen solution (350 milligrammes per 100 millilitres) to alter the clot dissolution when added to an equal volume of the patient's whole blood prior to clotting. Since polycythæmia was not present in this patient, a fibrinolysin was sought.

Lysis could not be demonstrated, either by Macfarlane's dilution technique (1937) or by the incubation of a mixture of the patient's serum and normal whole blood at 37° C. for forty-eight hours, though these methods have been used successfully by the authors in other cases of fibrinolysis. Incubation of equal volumes of the patient's whole blood and normal plasma or serum for twenty-four hours at 37° C. resulted in clot dissolution and red cell "fall out". It was thought that the lytic agent might be associated with the presence of the patient's formed elements; so a series of experiments was carried out with the patient's blood cells and those of a normal control. One-half of a millilitre of normal plasma was placed in each of six Lee and White coagulation tubes. To each of the first two were added 0·5 millilitre of the patient's red cells, to each of the next two 0·5 millilitre of the patient's platelet-rich plasma, and to each of the next two 0·5 millilitre of the patient's red and white cells. The mixtures were clotted by the addition of fifty units of "Topical Thrombin" (Parke, Davis and Company) and incubated for twenty-four hours at 37° C. The experiments were set up in duplicate with normal controls. In those tubes which contained the patient's red cells the clots were small and fragile and showed red cell "fall out", whereas the remaining tubes showed normal clots.

These experiments were repeated seven and fourteen days after the initial series, but the results previously obtained could not be reproduced. This may be explained by the fact that the initial experiments were performed when the patient was in a severe bleeding phase, whereas the later experiments were carried out when the patient had received treatment and was asymptomatic. It has been noted by Tagnon (1953) that cyclic variations in fibrinolytic factors can occur in cases of carcinoma of the prostate in which a bleeding diathesis existed. Unfortunately the patient lives in a remote area of Australia and is unavailable for long-term study.

DISCUSSION

The four patients described by Gardner and Diamond were women, aged from nineteen to sixty years, whose history of bleeding episodes ranged from four to twenty years. They all had a history of an injury causing bruising prior to the onset of their bleeding tendency, and it was postulated that this injury was the initial sensitizing stimulus. The presence of traumatic and spontaneous painful ecchymoses was an outstanding clinical feature, and many major bleeding episodes occurred, including intracranial hæmorrhage in two cases. A comparison of the symptoms of their patients and ours is shown in Table III.

TABLE III

Comparison of Clinical Features with Those of Reported Cases

Clinical Features	Gardner and Diamond's Cases				Present Case
	1	2	3	4	
Injury preceding the onset of bleeding episodes	+	+	+	+	+
Painful bruises	+	+	+	+	+
Intracranial bleeding	+	−	−	+	+
Urinary tract bleeding	+	−	−	−	−
Abdominal pain	+	−	+	+	−

Investigations by Gardner and Diamond showed that their patients were sensitive to the intradermal injection of 0·1 millilitre of their own whole red cells or red cell stroma, but were insensitive to hæmoglobin, plasma, plasma fractions or serum. The degree of cutaneous response was determined by the quantity of red cells injected; and they found that no patient had an abnormal response until the hæmatocrit was 20%, but above this level the response increased with the rising hæmatocrit. Gardner and Diamond suggested that the intradermal injection of the patient's whole blood provided a simple screening test.

Spontaneous fibrinolysis can be associated with chronic bleeding diathesis as in carcinoma of the prostate (Tagnon *et alii*, 1953), rarely without associated disease (Firkin *et alii*, 1955) and acutely in shock and pregnancy (Weiner *et alii*, 1950; Reid *et alii*, 1953; Hodgkinson *et alii*, 1954).

In the study of these cases the macroscopic appearances of the whole blood clot dissolution and red cell "falling out" was identical with the appearances found in this patient's blood, but the laboratory findings in her case were not similar, in that clot dissolution could be demonstrated only in the presence of her formed elements.

Gardner and Diamond noticed that a traumatic bruise frequently preceded the spontaneous bleeding episodes, which arose in sites

far removed from the original trauma, and they were unable to explain this adequately. They postulated that following physiological tissue bleeding extravascular concentration of red cells occurred and resulted in the autosensitization response, which, they postulated, may reflect itself in a generalized increase of vascular permeability. In our patient the autoerythrocytic response following trauma may have activated a fibrinolytic factor on her red cells, which rendered her more liable to spontaneous ecchymoses. Unfortunately routine coagulation studies in Gardner and Diamond's series did not include a search for fibrinolysis; so that it is impossible to say whether a fibrinolytic factor played any part in the spontaneous bruising in their patients.

The demonstration of autosensitization to a patient's own red cells creates a situation analogous to that seen in acute autoimmune hæmolytic anæmia. The red cells of autoimmune hæmolytic anæmia are usually coated with γ globulin, as detected by the Coombs antiglobulin reaction, whereas in autoerythrocyte sensitivity this reaction is negative. The sensitivity to cells other than our patient's own cells suggests that the fault lies in the tissues and not in the red cells, which, however, carry the antigenic material in the stroma.

The painful nature of the lesions in this condition is a diagnostic feature. In a study of over one hundred patients with various bleeding disorders ranging from hæmophilia to an acquired circulating anticoagulant, we have not found pain to be an outstanding feature of bruises of comparable size and anatomical site. The occurrence of intense itching and pain on intradermal injection of the patient's own red cells was of particular interest, since an injection of control cells of the same blood group did not cause this response, although the two injections resulted in comparable areas of bruising.

The relationship between erythrocyte sensitization and the fibrinolytic factor is difficult to define. That a common ætiological basis may exist is suggested by the fact that the lytic factor appeared to be associated with the formed elements of her blood and not in her plasma or serum. These findings, however, were not conclusive. Two mechanisms may be involved in the autoerythrocyte sensitization response; firstly, the release of a histamine-like substance from local tissue hypersensitivity resulting from the presence of the patient's red cells and causing the pain; secondly, the activation of a fibrinolytic factor, which is adsorbed to the patient's red cells and results in the local and more distant bleeding phenomena.

The investigations of Macfarlane *et alii* (1946) have led to the better understanding of the factors which inhibit fibrinolysis, and the demonstration of the inhibiting power of albumin has led to its therapeutic use by us in the treatment of bleeding associated with fibrinolysis. After the administration of 25 grammes of human serum albumin, the patient commented that the lesions became less painful and appeared to resolve more quickly, and fewer bruises appeared in the next four to five days. Objectively her blood clot was firm and showed little evidence of fibrinolytic digestion.

Remission in bleeding was noted in three of Gardner and Diamond's four cases, but without obvious relationship to therapy, and splenectomy induced no lasting benefit in two of their patients. Gardner and Diamond commented upon the subjective improvement in one patient whilst receiving cortisone therapy, and there was less pain and accelerated resolution of the bruises. Our patient gained no benefit from cortisone—indeed, bruises occurred more often; but the infusion of 25 grammes of human serum albumin on three separate occasions produced subjective improvement, decreased bruising for four or five days, and decreased fibrinolysis *in vitro*. We consider that albumin infusion may be of value in phases associated with acute bleeding as a safeguard against cerebral hæmorrhage; in-vitro effect was clearly shown at the end of twenty-four hours (Figure IV), and clinically the bruises were lessened for four or five days.

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URIC ACID AND THE URICASE-RESISTANT RESIDUE IN RENAL INSUFFICIENCY[1]

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SUMMARY

After the destruction of uric acid in blood serum with the enzyme uricase, there remains a uricase-resistant chromogen, which reacts with the phosphotungstate reagent used for uric acid determinations.

Expressed as uric acid, the amount of this chromogen was almost negligible in 45 normal subjects, but was greatly increased (that is, up to eight milligrammes per 100 millilitres of serum) in renal insufficiency. Still higher values were encountered in a case of lethal eclampsia.

In two cases of renal failure serial determinations of this chromogen were made, and it appeared to vary with the severity of the disease. The nature of this substance, which may play a significant role in the pathogenesis of renal failure, is unknown.

THE occurrence of elevated amounts of uric acid in the blood of patients with renal insufficiency has long been known, and values above 20 milligrammes per 100 millilitres have frequently been recorded in contrast to the upper normal limit of approximately 6·0 milligrammes per 100 millilitres. When the specific enzyme uricase, which oxidizes uric acid to the non-chromogenic allantoin, was used in conjunction with the usual colorimetric method (Folin, 1933), it became evident that a considerable fraction of the total chromogen content in the blood of nephritics is in fact not uric acid. This fraction, the uricase-resistant residue or chromogen, consists of substances of unknown nature. Uric acid, uricase-resistant residue and total phenols were determined in a series of normal subjects and hospital patients without and with renal insufficiency, and in cases of pregnancy toxæmia. In addition, almost daily determinations were done in two cases of renal insufficiency over a period of several weeks.

[1] Received on June 21, 1956.

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METHODS

Serum was used throughout. Direct uric acid values were determined by the method of Folin (1933). In order to obtain a satisfactory blank, the commercially available sodium cyanide was recrystallized from water. Five hundred grammes of the salt were dissolved in 400 millilitres of hot water. The recrystallized sodium cyanide was kept in a desiccator over sodium hydroxide pellets.

True uric acid content was evaluated according to the method of Blauch and Koch (1939). The difference in colour values before and after treatment with uricase was considered to be a measure of the true uric acid content of the serum.

The uricase-resistant chromogen or residue is the residual colour remaining after the action of uricase and is expressed as uric acid.

Phenols were determined by the method of Folin and Ciocalteu (1927).

RESULTS

The findings on sera from 45 normal subjects and from patients without renal insufficiency or disturbances of purine metabolism are listed in Table I.

Patients with Renal Insufficiency

The figures in Table II were obtained from 11 patients; in six of these the main diagnosis

was chronic nephritis, three had pyelonephritis, and one had crush uræmia.

Toxæmia of Pregnancy

Five patients with toxæmia of pregnancy had the serum values shown in Table III.

Eclampsia

A *primipara*, aged twenty-eight years, suffering from eclampsia, had a direct uric acid content of 21 milligrammes per 100 millilitres on the day before death, but the true uric acid content was only 6·0 milligrammes per 100 millilitres, leaving a uricase-resistant residue of 15·6 milligrammes per 100 millilitres. The total phenol content was 20 milligrammes per 100 millilitres. A patient with eclampsia of short duration starting four hours *post partum* (twin birth) had a direct uric acid value of 13·4 milligrammes per 100 millilitres and a uricase-resistant residue value of 4·3 milligrammes per 100 millilitres.

TABLE I

Results in 45 Control Subjects

Determination	Average (Milligrammes per 100 Millilitres)	Range (Milligrammes per 100 Millilitres)
Direct uric acid	3·9	1·8 to 5·9
True uric acid	3·6	1·7 to 5·6
Uricase-resistant residue	0·2	0·0 to 0·5
Total phenols	3·7	2·5 to 5·0

TABLE II

Results in 11 Patients with Renal Insufficiency

Determination	Average Milligrammes per 100 Millilitres)	Range (Milligrammes per 100 Millilitres)
Direct uric acid	13·5	7·2 to 18·0
True uric acid	9·5	6·8 to 15·0
Uricase-resistant residue ..	4·0	0·6 to 7·9
Total phenols..	10·8	8·0 to 14·0
Blood urea	382·0	150·0 to 590·0

Individual Cases of Renal Insufficiency Observed over Several Weeks

A male patient, aged forty years, who had suffered a severe crush injury, developed marked oliguria and urea retention. Four days after the accident, when our observations began, the blood urea content was 260 milligrammes per 100 millilitres and the direct uric acid content was 14·2 milligrammes per 100 millilitres, while the true uric acid content and the phenol content were each 9·8 milligrammes per 100 millilitres. For the next six days the levels of these blood constituents rose further, as depicted graphically in Figure I. Then the uric acid and phenol levels began to fall as well as the urea level. Eighteen days after the accident the values for uric acid and phenols were within normal limits, and the patient had completely recovered. Up till then there existed a marked difference between the direct and the true uric acid values, which reached a maximum of 4·8 milligrammes per 100 millilitres (Figure I). After that the level of uricase-resistant residue fell to zero, and the two uric acid values became identical.

The serum of a woman, aged forty-eight years, who was suffering from chronic nephritis and was in uræmic coma at the beginning of the investigation (her blood urea content was 475 milligrammes per 100 millilitres), showed a sharp rise in direct uric acid content (19 milligrammes per 100 millilitres), while the urea content increased to nearly 600 milligrammes per 100 millilitres, as depicted in Figure II. This was followed by a relative drop and then a further rise in both the direct and true uric acid values, while the phenol and direct uric acid values as well as the urea content dropped in the second half of the observation period. Attention is drawn to the large uricase-resistant residue, which reached a maximum of 7·9 milligrammes per 100 millilitres. Coincidently with some clinical improvement the uricase-resistant residue became smaller (Figure II).

TABLE III

Results in 5 Patients with Toxæmia of Pregnancy

Determination	Average (Milligrammes per 100 Millilitres)	Range (Milligrammes per 100 Millilitres)
Direct uric acid	7·7	5·6 to 10·2
True uric acid	4·6	3·1 to 6·6
Uricase-resistant residue ..	3·3	1·7 to 4·5
Total phenols..	5·0	4·0 to 5·9

DISCUSSION

The direct uric acid content of blood serum is usually above normal limits in patients with moderate and particularly with severe renal impairment. The same applies to the true uric acid content, which, however, in severe renal insufficiency is always appreciably lower than that of direct uric acid. The difference between the two values is represented by the uricase-resistant residue, which consists of substances chemically not related to uric acid. This uricase-resistant residue increases in cases of renal insufficiency, as do some nitrogenous constituents of the blood, such as urea, uric acid *et cetera*. This increase may be 20 to 30 times as large as the average normal value.

The maximum theoretical solubility of sodium urate in serum has been calculated as 6·4 milligrammes per 100 millilitres expressed as uric acid. Experimentally it was found to be

about 8·0 milligrammes per 100 millilitres. This is in sharp contrast to the frequently reported direct uric acid values of 20 to 30 milligrammes per 100 millilitres in cases of severe renal insufficiency. By the uricase method we found in cases of severe urea retention of over 400 milligrammes per 100 millilitres true uric acid values between 6·8 and 15 milligrammes per 100 millilitres—that

Considerable criticism has been levelled at the colorimetric methods for the determination of blood uric acid content, and it has been claimed that they lack specificity and that the development of the colour due to uric acid is inhibited by other compounds present in the blood. In spite of this, colorimetric procedures are still used predominantly in biochemical laboratories all over the world. The specificity

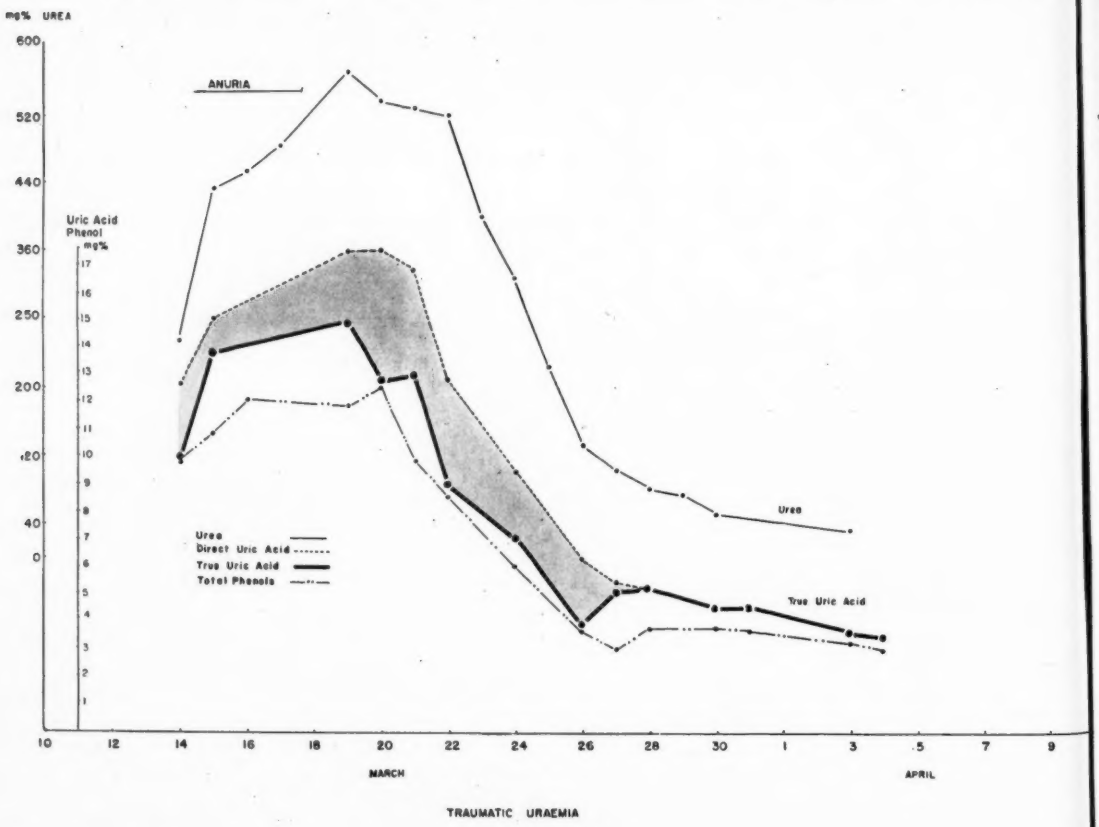

FIGURE I

Blood chemistry findings in a case of traumatic uræmia with complete recovery. The shaded area between the values for total and true uric acid represents the uricase-resistant residue in blood serum

is, figures frequently in excess of theoretical as well as experimental findings. This could be explained by supersaturation of uric acid, which may become greater with the altered conditions in uræmic sera compared with normal sera, such as reduction of total serum protein values and alterations in the albumin-globulin ratio. However, we should like to put on record that the highest true uric acid value found did not exceed 15 milligrammes per 100 millilitres.

of the method is increased considerably by using the enzyme uricase, which selectively destroys uric acid. Blauch and Koch (1939) were the first to apply this method to the serum of normal subjects, but this procedure has not been used for sera of persons with marked nitrogen retention. Emphasis was placed on true uric acid values, and the significance of the uricase-resistant residue was ignored.

Some of the uricase-resistant substances are no doubt phenolic in character, because certain phenols occurring in the body, such as tyrosine, strongly react with the phosphotungstate reagent of Folin. In the present study phenols were determined to investigate whether a direct relationship existed between total phenol and uricase-resistant chromogen values. No such direct parallelism could be observed, although phenols were increased in amount during nitrogen retention.

True uric acid values are still under a cloud of suspicion and await confirmation by recently described spectrophotometric methods. The uricase-resistant chromogen value, however, cannot be determined by the spectrophotometric method and depends on colorimetric estimations. In cases of renal insufficiency this uricase-resistant residue becomes prominent and increases to a relatively larger extent than the other constituents of the blood usually determined. In fact, an elevated uricase-resistant residue was sometimes the only finding in conditions such as the milder type of chronic nephritis and toxæmia of pregnancy, in which urea and uric acid may be within normal limits. The highest uricase-resistant residue was found in a lethal case of convulsive toxæmia of pregnancy in a young woman. Here it was about 75 times as high as in normal subjects, and it becomes clear that the frequently reported hyperuricæmia of pregnancy toxæmia is to a large extent due to substances other than uric acid. They are, as yet, of unknown nature, and it may well be possible that the much sought-for toxin of eclampsia is among the compounds responsible for the exceptionally high uricase-resistant residue. In cases of renal failure from other causes the large uricase-resistant residue may play a similar toxic role.

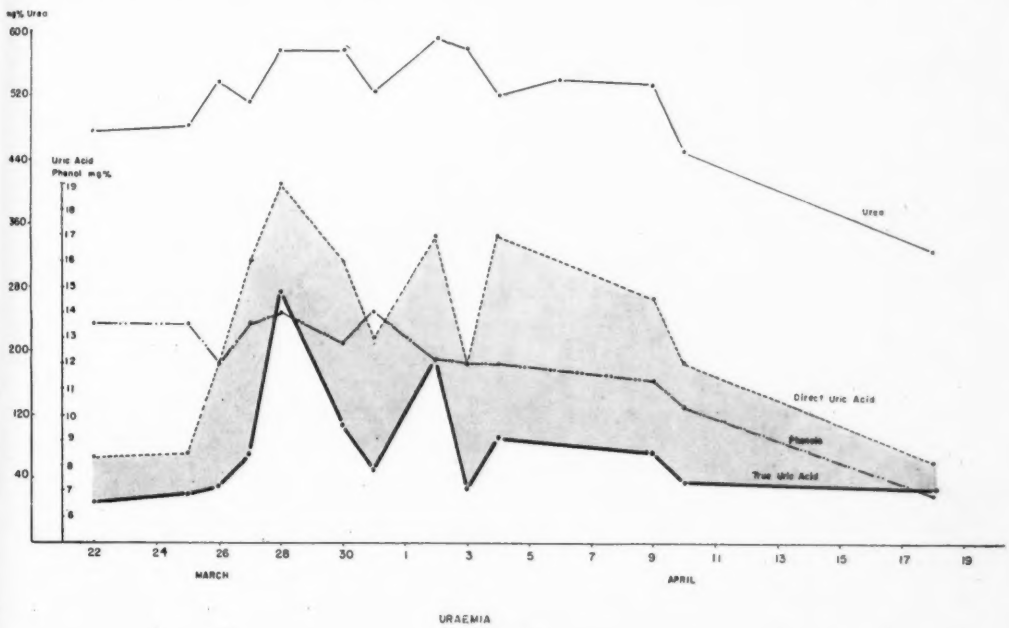

FIGURE II

Blood chemistry findings in a patient with severe uræmia. The shaded area between the values for total and true uric acid represents the uricase-resistant residue in blood serum

ACKNOWLEDGEMENTS

We are greatly indebted to Dr. K. M. Mattocks, Chemical Pathologist to the Royal Prince Alfred Hospital, Camperdown, for the supply of specimens.

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THE PATHOGENESIS OF ULCERATIVE COLITIS[1]

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Summary

The pathogenesis of ulcerative colitis has been interpreted in terms of histamine-release phenomena. The dominant alterations of the colon are congestion and œdema. These, together with muscular excitation, can be explained in terms of the known effects of histamine-release agents in experimental animals. Superficial ulceration is thought to be due to simple excoriation of œdematous and congested mucosa. Deep ulceration probably arises from strains due to stretching of the mucosa where it is more firmly attached over the muscular tæniæ and in the crypts between the rugæ.

In support of this interpretation is the relative absence of inflammatory cells in the submucosa until ulceration occurs. The nature of the syndrome is thought to be within the realm of the psychosomatic disorders. Augmented barrages of nervous impulses during stress may give rise to excessive production of acetylcholine in the colon, which then reacts with the tissue mast cells causing the phenomenon of " histamine-release ". Return to normal does not take place when the stress passes if the congestion and œdema have been present for long enough to permit some fibrosis to occur in the submucosa.

Although most clinicians agree that mental stress is an important ætiological factor in the background of ulcerative colitis, there has been no satisfactory explanation of the mechanism by which the pathological changes are brought about. In this paper, it is postulated that the alterations in the bowel are the consequence of functional disorder and an attempt is made to elucidate the mechanism.

Materials

During the past six years, surgical resection of the colon for ulcerative colitis has been performed on 32 occasions at the Royal Prince Alfred Hospital. During the same period there were 20 autopsies in which ulcerative colitis was the principal pathological finding. Specimens from these cases form the basis of this study.

Pathology

Characteristically, this disorder affects the large bowel. It seems often to start in the pelvi-rectal segment and gradually extends back towards the cæcum. In very severe cases the terminal two or three feet of the ileum are involved in the reaction.

The fundamental changes in the gut are congestion and œdema, together with some muscular spasm and hypertrophy. The congestion and œdema affect all coats, but are most prominent in the submucosa which normally has a fairly loose structure (Figure I). Although plasma cells and eosinophile cells may be fairly numerous in the mucosa and a few may be present in the submucosa, a typical acute cellular reaction occurs only when ulceration is present.

Ulceration

Ulceration may be superficial or deep. Superficial ulceration is probably due to the excoriating action of the intestinal contents hurrying over the congested and œdematous mucosa. This type of ulceration does not penetrate the *muscularis mucosæ*.

A consideration of the anatomy of the colon is necessary to understand the mechanism of deep ulceration. Just as the creases of the palm of the hand are due to the skin's being uniformly bound in a linear fashion to the deep fascia, so the mucosa is more firmly bound to the muscular coat in the troughs between the transverse rugæ. Overlying the muscular tæniæ, the mucosa is similarly attached.

As the horizontal mucosal folds become more and more swollen, the troughs between them are converted into narrow clefts and the mucosa in the depths of the clefts appears to

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be stretched (Figure I). Eventually a break occurs and ulceration ensues (Figure II). Similarly, as the œdema of the mucosa advances, longitudinal gutters appear over the muscular tæniæ (Figure III). Later, ulceration occurs and the ulcers so formed may extend for several inches (Figure IV).

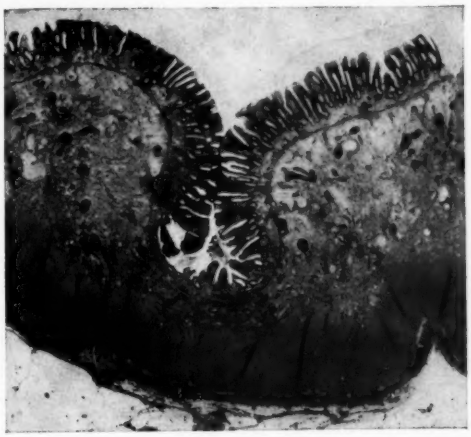

FIGURE I

Section of non-ulcerated portion of colon in a fulminant case. Congestion and œdema of submucosa are very prominent. At the bottom of the trough between two horizontal rugæ, the mucosa is being stretched and is on the point of ulcerating. (Hæmatoxylin and and eosin stain, ×7)

Ulceration sometimes seems to occur by reason of abscesses forming in the depths of mucosal tubules. These may coalesce and thus undermine adjacent mucosa.

Once ulceration of the deep type has been established, it extends into the submucosa, undermining the adjacent œdematous mucosa, with the result that much of the latter is cast off. That which remains presents a polypoid appearance. These polypi are therefore œdematous mucosal tags (Figures V and VI). Occasionally this deep type of ulceration penetrates the muscular coats of the intestine and extends into the subserous tissues (Figure VII). With the advent of ulceration polymorphonuclear leucocytes make their appearance.

In the severe fulminating case, deep ulceration of the linear type overlying the muscular tæniæ and deep circumferential ulcers can be expected. In the less severe case in which there have been remissions, the ulceration is usually of the superficial type only. In cases of intermediate severity both types of ulceration may be present.

The muscular coats of the colon appear hypertrophied. In all probability this is mainly due to spasm. However, there is little shortening, because of the splinting effect of the œdematous mucosa and submucosa. The serous coat, too, becomes congested and œdematous.

HEALING

Healing can occur to a remarkable extent during remission. Epithelium creeps across from the intact mucosa, and a simplified form of glandular mucosa results. *Muscularis mucosæ* cannot be regenerated, so the epithelium grows down into the ulcers (Figure VIII). The submucosa does not revert to normal, but remains somewhat congested and œdematous. A mild degree of fibrosis occurs in the œdematous submucosa, and during a remission adipose tissue and lymphoid follicles appear, which all contribute towards the

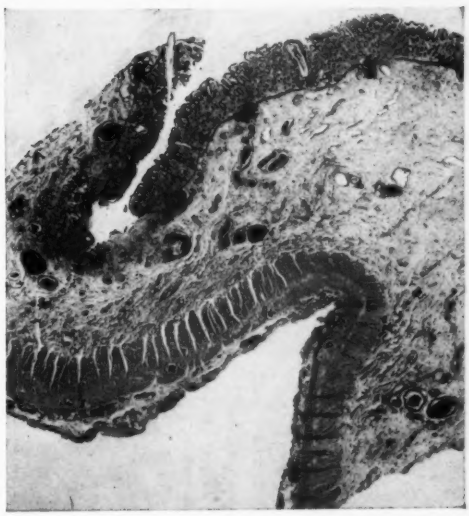

FIGURE II

Showing early ulceration of the deep type in the crypt between two rugæ in the ascending colon in a fulminant case. (Hæmatoxylin and eosin stain, ×7)

maintenance of its abnormal thickness (Figure IX). When there has been merely superficial ulceration, lymphoid follicles are found in the mucosa and are responsible for the mammellated appearance which the mucosa sometimes has during a remission. If the ulceration has been particularly deep, the regenerating mucosa may lie upon the inner circular muscle coat, or even upon subserous tissues.

FIGURE III

Descending colon during quiescent phase. There has been only superficial ulceration in this case. The œdematous mucosa accentuates the longitudinal gutters where the mucosa is more firmly bound to the underlying muscle

FIGURE IV

Early longitudinal ulceration of the deep type occurring in the ascending colon in a severe case

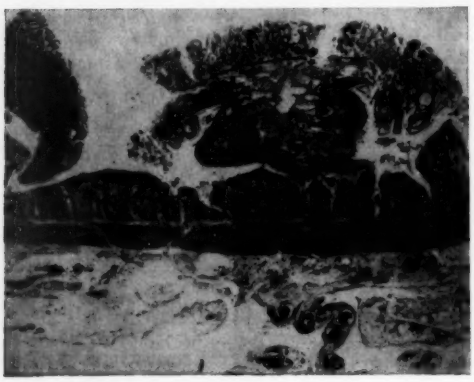

FIGURE V

Illustration of the undermining character of the deep ulceration with polypoid tags of surviving mucosa. (Hæmatoxylin and eosin stain, ×6)

FIGURE VI

A polypoid nodule during a remission. There is some epithelial hyperplasia, and epithelium is attempting to grow down on to the surface of the ulcers. (Hæmatoxylin and eosin stain, ×7)

FIGURE VII

Deep ulceration which has penetrated the muscularis into the subserosal layer. There is fairly prominent fibroblastic granulation tissue forming the base of the ulcer. (Hæmatoxylin and eosin stain, ×9)

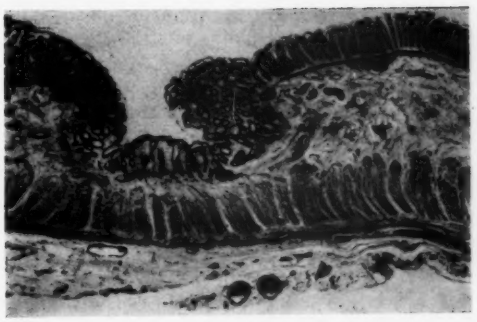

FIGURE VIII

Healing of a deep ulcer. A simplified layer of epithelial tubules has grown down to cover the ulcerated area. (Hæmatoxylin and eosin stain, ×10)

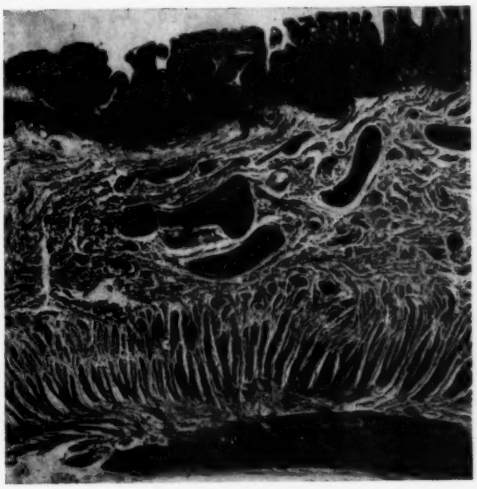

FIGURE IX

Healing of superficial ulceration. Lymphoid tissue is very prominent in the *lamina propria* and projects into the superficial part of the submucosa. The regenerated mucosa has a simplified form. The submucosa is still congested. Fibrous tissue in the submucosa maintains the abnormal thickness. (Hæmatoxylin and eosin stain, ×7·5)

FIGURE X

The terminal portion of the ileum from a patient in remission. Distally there are numerous small nodules which diminish in number proximally. These nodules indicate the extent of ileal involvement

Ulceration in the ileum, when it occurs, is of the transverse type, there being no muscular tæniæ. During a remission, small sessile nodules due to hypertrophied lymphoid tissue in the ileum indicate the extent of the disease even when no ulceration has been present (Figures X and XI).

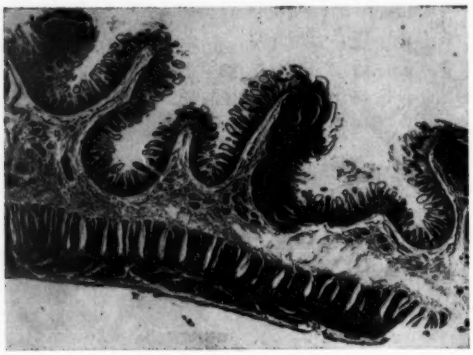

FIGURE XI

Microscopic appearance of the ileum illustrated in Figure X. The nodules are due to hypertrophied lymphoid tissue in the *lamina propria* of the mucosa. (Hæmatoxylin and eosin stain, ×5·5)

Summary

The pathological changes in ulcerative colitis can be summarized as being essentially congestion, œdema and muscular spasm, and ulceration is regarded as a complication following these changes.

The fundamental reactions in the gut are therefore typical of the so-called histamine-release phenomena.

MECHANISM OF HISTAMINE-RELEASE PHENOMENA

Histamine-release agents when injected into the tissues cause congestion, œdema and contraction of smooth muscle. Repeated injections deplete the tissues of histamine. Substances which act as histamine-release agents include ovalbumin, dextran, bile, acetylcholine and a number of synthetic compounds. After the clinical effect of injecting a histamine-release agent has subsided, the only change to be found in the tissues is depletion of the granules of mast cells (Riley, 1953). Mast cells are thought to yield heparin (Jorpes, 1946), histamine (Riley, 1953), and a substance causing increased permeability of capillary endothelium (McGovern, 1956*a*).

The rat is a convenient animal in which to demonstrate histamine-release phenomena. A peritoneal injection of egg white causes redness of the ears, feet and mouth regions, which presently become œdematous. Such congestion is thought to be due to histamine. Increased permeability is due to alterations in the consistency of the intercellular cement of the capillary endothelium (McGovern, 1956*a*). Peristaltic activity may be stimulated by released histamine, and bronchospasm can be induced when appropriate concentrations of histamine-release agents are brought into contact with the mast cells in the vicinity of bronchi.

CONCEPT OF HISTAMINE-RELEASE PHENOMENON APPLIED TO ULCERATIVE COLITIS

As has already been described, the most prominent features in the early stages of ulcerative colitis are congestion and œdema, which have been interpreted as representing a histamine-release phenomenon. It must be clearly understood in this paper that "histamine release" implies the liberation of heparin and the permeability factor from mast cells in addition to histamine.

The problem then arises as to the mechanism of histamine release in ulcerative colitis. The human intestine contains numerous mast cells,

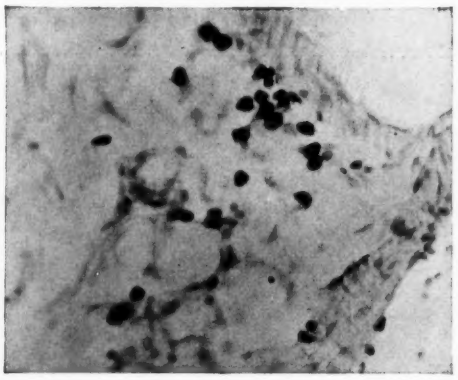

FIGURE XII

Submucosa of colon in ulcerative colitis, stained to demonstrate mast cells. (Giemsa stain, ×300)

particularly in the submucosa. They are usually scanty in the muscular coats, being found almost exclusively in the lontigudinal muscle layer. In ulcerative colitis, however, they are numerous in both muscle coats, and accompany vessels which penetrate the inner circular coat from the submucosa (Figures XII and XIII). Mast cells are therefore present in sufficient numbers to give rise to the phenomenon of histamine release.

Mast cell secretion normally seeps through the intercellular cement of capillary endothelium dissolving in it, and by virtue of the permeability factor regulates its consistency (McGovern, 1956*a*). If the mast cells yield excessive amounts of secretion, as they do when brought in contact with the more powerful histamine-release agents, the consistency of the intercellular cement is altered to such an extent that fluids pass through into the surrounding tissues. Liberated histamine may cause vascular congestion and a spastic state of the colonic musculature that is akin to bronchospasm in asthma. This continuous contraction of the muscle, together with the congestion and œdema of the mucosa and submucosa, would convert the colon into a thick-walled, semi-rigid tube which no longer contracts segmentally, and haustrations are lost.

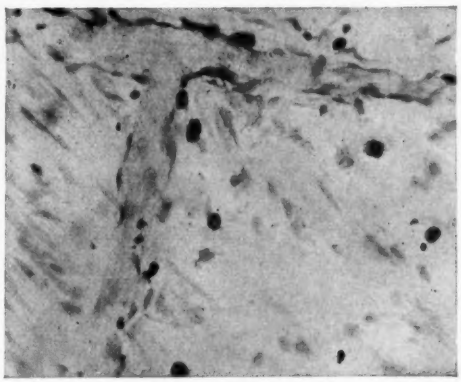

FIGURE XIII

Mast cells accompany a small vessel entering the muscularis from the submucosa of the colon in ulcerative colitis. (Giemsa stain, ×300)

Heparin, the third component of mast cell secretion, bears a negative electrical charge (Jorpes, 1946), and is soluble in the intercellular cement of vascular endothelium (Samuels and Webster, 1952). In this way a negatively charged film is maintained which repels particles such as leucocytes which, according to Abramson (1925, 1927), are also negatively charged. With severe injury as in ulceration, vascular endothelium loses its power to form adequate cement which is the vehicle for heparin. Leucocytes then accumulate upon the endothelial surface. An injury of this severity depletes the related mast cells, and, when they are exhausted, the heparin liberated in the vicinity gradually disappears and the injured tissues revert to their normal electrical potential which, in relation to vessel contents, has been shown by Abramson (1925, 1927) and by Sawyer and Pate (1953) to be positive. Leucocytes are then attracted into this positive zone, there being no negatively-charged cement film to impede them. In support of this concept, it has been found that local heparin injections prevent leucocytic migration after an injury which ordinarily causes a cellular inflammatory response (McGovern, 1956*b*).

The concept of histamine-release phenomenon as the basic lesion in ulcerative colitis accounts for the absence of inflammatory reaction until ulceration occurs.

PSYCHOSOMATIC CORRELATION

The question arises why only certain people develop ulcerative colitis. Some people have diarrhœa in adverse circumstances, while in others a different organ is affected. Though in general these reactions to stress seem to be of genetic origin, there is probably an anatomical reason for the individual variation in the organ which reacts. Whichever organ this may be is attuned to respond.

In ulcerative colitis it is conceivable that, during stress, augmented barrages of nervous impulses arriving in the colon liberate increased quantities of acetylcholine. Acetylcholine, a powerful histamine-release agent (McGovern, unpublished data), stimulates the mast cells to secrete at a greater rate than normal. As a result the reactions of the histamine-release phenomenon become manifest.

Factors other than mental stress may precipitate ulcerative colitis, but for the continuation of the disorder the mechanism of mental stress is probably necessary. Whether failure of suppressor activity of the brain permits increased nervous impulses to reach the colon, or whether the colon is unusually responsive in patients who develop ulcerative colitis, has not been determined.

ACKNOWLEDGEMENTS

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THE MECHANISM OF SODIUM RETENTION IN CIRRHOSIS OF THE LIVER WITH ASCITES: THE EFFECT OF ACETAZOLAMIDE (" DIAMOX ") ON URINARY ELECTROLYTES[1]

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SUMMARY

Acetazolamide is shown to increase the urinary excretion of sodium and the sodium to potassium ratio in seven normal subjects and five cirrhotic patients without ascites. In seven cirrhotic patients with ascites the urinary output of sodium and the sodium to potassium ratio were low initially, and were unchanged by acetazolamide.

The subjects with ascites had no evidence of renal disease, and the failure to excrete sodium must be attributed to an extrarenal factor. These observations are compatible with the hypothesis that there is an excessive secretion of aldosterone, though they do not indicate the cause. It is not necessarily lowering of plasma sodium level, as the abnormality of sodium and potassium excretion was also noted in one subject with a high normal plasma level. Liver disease also is not essential, as similar sodium retention occurred in one subject whose ascites was due to extrahepatic portal hypertension.

Acetazolamide is found not to be a good diuretic in patients suffering from liver disease.

IT is well known that in a cirrhotic patient with tense or rapidly accumulating ascites, the output of sodium in the urine is negligible irrespective of the dietary content of sodium. It was shown, for instance, by Eisenmenger *et alii* (1950) that the twenty-four-hour urinary sodium output in such cases is less than four milliequivalents, sometimes even less than one milliequivalent. Improvement of liver function and diminution of ascites is accompanied by a gradual return to normal of urinary sodium excretion. In the stage of maximal sodium retention, orally administered sodium is retained in the body, together with an amount of water which would contain the sodium in isotonic dilution. While the ultimate mechanism of sodium retention is clearly renal, there has been considerable confusion regarding the part played by altered circulatory dynamics within the kidney itself. Leslie *et alii* (1951) claimed that the glomerular filtration rate and renal blood flow were uniformly depressed in cirrhotic patients with ascites, and Pitts and Duggan (1950) noted that even moderate reduction of glomerular filtration could greatly restrict the capacity of the kidney to excrete electrolyte and water. Others, however, have found normal figures for renal blood flow and glomerular filtration (Epstein *et alii*, 1950; Goodyer *et alii*, 1950). The whole question has been reviewed recently by Gilder *et alii* (1956), and there seems little doubt that in most cases alterations in renal circulatory dynamics play a minimal, if any, part in either instituting or maintaining the retention of sodium and water.

Eisenmenger *et alii* (1950) also found that, in cirrhotic patients with ascites, the ratio of sodium to potassium was greatly decreased in sweat and saliva as well as in urine. This suggested that some circulating hormonal influence was responsible for these changes. As the presumed site of action of such a hormone is on the renal tubule cell, it was thought that useful information might come from a study of urinary electrolytes after the administration of a drug which is a sensitive agent for assessing variations in renal tubule cell function. Acetazolamide (2,acetylamino-1,3,4-thiadiazole-5-sulphonamide; " Diamox ", Lederle) was thought by Counihan *et alii* (1954) to be such a drug. It is a specific carbonic anhydrase inhibitor, and its basic effect is to increase bicarbonate excretion by decreasing its normal tubular reabsorption. The increased bicarbonate excretion results in increased cation excretion, and the two most important cations in this respect are sodium and potassium. The relative amounts of each excreted will depend upon other hormonal influences which control their reabsorption in the renal tubule. Thus, " Diamox " does not act primarily on

[1] Received on July 25, 1956.

sodium or potassium, but its effect of increasing bicarbonate excretion necessitates increased cation excretion, and will tend to counteract the influence of any sodium-retaining factor on the renal tubule, and to exaggerate that of any potassium-losing factor. It was therefore felt that it would be of interest to study the excretion of sodium and potassium in the urine before and immediately after the administration of " Diamox " to cirrhotic patients with ascites. The results would best be expressed as a ratio of sodium to potassium. Studies were made on a control group of normal subjects, a group of cirrhotic patients with or without ascites, and a third group of ascitic patients without liver disease.

This study provided an opportunity of assessing the importance of the plasma sodium level in controlling the urinary output of sodium, and also the clinical value of " Diamox " as a diuretic in patients with liver disease.

METHODS

Patients studied were divided into the following four groups (the clinical and laboratory features of the last three groups are summarized in Tables I and II).

(*a*) *Normal Controls* (seven subjects). These were members of the hospital staff (six) and one patient convalescent from infectious mononucleosis. All were without evidence of disease of the liver, kidneys or cardio-vascular system.

(*b*) *Cirrhosis of the Liver Without Ascites* (five patients). The diagnosis had been confirmed in this group by hepatic biopsy. One patient (Number 8, F.K.) had been ascitic, but had responded to a diet of low sodium content, and dietary sodium restriction was being relaxed when these investigations were made.

(*c*) *Cirrhosis of the Liver With Ascites* (seven patients). Three of these patients had biopsy confirmation of the diagnosis, while in the remaining four the presumptive diagnosis is based on the clinical and laboratory findings (Tables I and II).

(*d*) *Portal Hypertension and Ascites due to Extrahepatic Portal Obstruction* (two patients). Both of these patients had normal findings from liver biopsies. One (Number 20, H.T.) had had intractable ascites for three years, while in the other the ascites was of short duration and more readily controlled. The diagnosis in both patients had been confirmed by transsplenic portal venography.

TABLE I

Clinical Features

Subject	Age (Years)	Sex	Spider Angiomata	Palmar Erythema	Liver Enlargement[1]	Spleen Enlargement[1]	Hepatic Fœtor	Hepatic Biopsy Finding
				Group B				
8	35	M.	0	0	1	2	0	Portal cirrhosis
9	19	F.	0	0	0	2	0	Portal cirrhosis
10	38	M.	+	+	2	0	+	Portal cirrhosis
11	43	F.	H.H.T.[2]	+	3	2	0	Portal cirrhosis
12	46	M.	0	±	2	1	0	Portal cirrhosis
				Group C				
13	50	F.	+	+	0	0	+	—
14	49	M.	+	0	2	1	+	—
15	53	F.	0	+	0	0	+	Portal cirrhosis
16	57	M.	+	+	0	2	+	—
17	51	F.	+	+	0	2	+	—
18	42	F.	+	0	5	0	0	Portal cirrhosis
19	72	F.	0	+	2	1	+	—
				Group D				
20	64	M.	0	0	0	2	0	Normal liver
21	78	F.	0	0	0	0	+	Normal liver

[1] Finger's breadth beneath the costal margin.
[2] Hereditary hæmorrhagic telangiectasia.

Primary renal disease was excluded as far as possible in all cases. The urine of patients belonging to all groups was free of albumin to regular routine ward testing, and random measurements of specific gravity of early morning specimens exceeded 1020 at least once in every case. Microscopic examination and culture, where carried out, showed no abnormality.

"Diamox" (250 milligrammes) was given orally, and two-hourly urine samples were collected for two hours before and for eight hours after the test dose was given. Patients were given 200 millilitres of water at the commencement of the first collection period to encourage urinary output, but thereafter were allowed food at the normal times and fluid as desired. They were all at bed rest except six of the control subjects, who, being hospital staff, continued their normal duties. Subjects received a standard hospital diet with unrestricted sodium intake. The ascitic patients received a diet of low sodium content (22 milliequivalents per day or less) with six grammes of added sodium chloride daily for the two days before and the day of the test. The volume and the sodium, potassium and bicarbonate contents of each two-hourly urine specimen were estimated.

The plasma sodium level and twenty-four-hour urinary sodium output have been correlated only in the patients in the ascitic group C, and in the one ascitic patient in group B (Number 8, F.K.) during the period while he was actively forming ascites. This study was also made on eight additional ascitic patients, the terminal stages of whose disease have been described elsewhere (Hecker and Sherlock, 1956). Blood and twenty-four-hour urine samples were taken on the same day; and where significant alterations in the plasma sodium level occurred as the disease progressed

TABLE II

Routine Biochemistry Findings

Subject	Serum Values							Plasma Values					
	Bilirubin (Milligrammes per 100 Millilitres)	Cholesterol (Milligrammes per 100 Millilitres)	Alkaline Phosphatase (King-Armstrong Units)	Thymol Turbidity (Units)	Zinc Sulphate (Units)	Albumin (Grms. *per Centum*)	Globulin (Grms. *per Centum*)	Prothrombin Time (Seconds)	Sodium (Milliequivalents per Litre)	Potassium (Milliequivalents per Litre)	Chloride (Milliequivalents per Litre)	Bicarbonate (Milliequivalents per Litre)	Urea (Milligrammes per 100 Millilitres)
Normal values	0·1–0·8	123–324	3–13	0–4	4–12	4·0–5·7	1·5–3·0	12	133–152	3·5–5·6	99–108	24–31	12–47
Group B													
8	0·3	225	9·2	3·5	8	4·1	2·8	—	140	4·0	105	—	41
9	1·5	331	28·8	36	24	3·6	4·6	15	138	4·8	105	25	38
10	5·6	244	18	21	24	3·4	4·3	14	128	3·3	104	28·1	23
11	0·5	246	37·8	7	10	3·6	3·7	12	140	4·4	105·5	29	26
12	0·8	284	15·0	8	2	3·4	4·3	12	—	—	—	—	—
Group C													
13	1·2	322	21·3	9	8	3·2	3·0	16	128	2·4	103·4	24·1	95
14	1·9	190	23	18	3	2·7	3·9	8	141	3·5	103	27·2	23
15	0·9	286	18	1	6	3·9	3·2	14	145	4·5	107	19·2	55
16	0·6	—	13·5	10	24	2·8	4·1	12	133	3·3	110	25·2	48
17	0·5	294	20·5	1	3	2·9	2·9	13	140	3·4	110	25·3	31
18	2·1	288	26	2	8	2·7	4·4	12	134	3·5	102·5	25	32
19	0·4	200	6·3	1	8	3·4	3·5	15	140	3·2	107	27·9	18
Group D													
20	0·4	262	—	0	12	2·5	4·8	13	135	4·5	88	34·2	54
21	0·8	310	10·3	1	6	3·3	3·3	13	120	3·0	107	21·2	34

(four patients), two sets of figures have been included for these patients, one on admission to hospital and the other in the terminal stages of the disease (Table IV, Figure III). Except for the figures taken during the terminal stages of the illness of these four patients, the

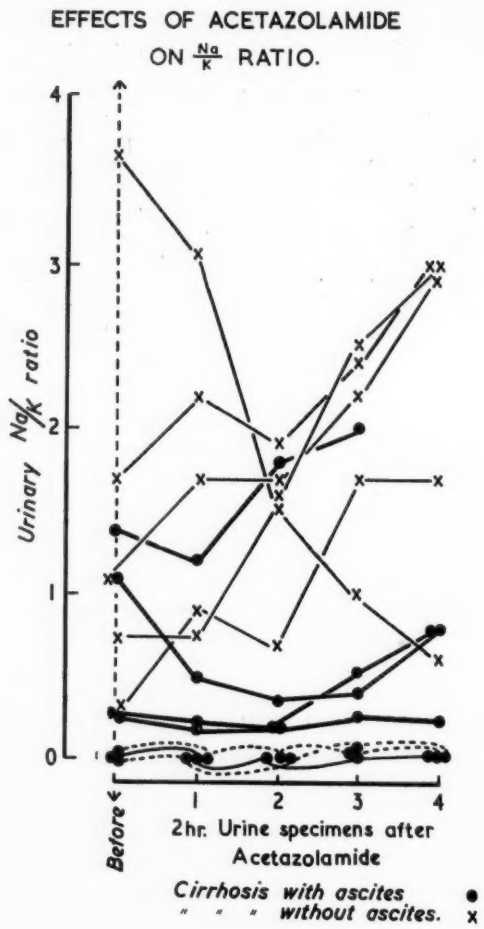

FIGURE I

patients were receiving a diet of unrestricted sodium content. No diuretics were administered just before or during urine collections.

Routine biochemical methods were used for all estimations. Plasma and urinary sodium and potassium contents were estimated with an Eel flame photometer, bicarbonate contents by the manometric Van Slyke method and chloride contents by the method of Sendroy (Sendroy, 1937) modified by Van Slyke and Hiller (Hawke *et alii*, 1947).

RESULTS

The sodium to potassium ratio in every two-hourly urine sample has been charted in Table III, and values for the two cirrhotic groups (B and C) have been graphed in Figure I. The preliminary sodium to potassium ratios were unequivocally lower in the ascitic groups (C and D) than in the non-ascitic ones (A and B). Whereas the ratios in the latter two groups tended to rise under the influence of " Diamox ",

TABLE III

Subject	Urinary Sodium to Potassium Ratios (Two-Hourly Periods)				
	Before Acetazolamide	After Acetazolamide			
		1	2	3	4
		Group A			
1	0·8	1·1	1·8	1·5	1·7
2	1·2	1·2	0·8	1·6	1·2
3	1·6	2·2	1·8	1·5	1·3
4	1·8	1·3	1·2	1·0	0·7
5	3·0	2·5	2·6	3·2	4·0
6	2·0	3·0	2·7	3·2	0·9
7	1·7	2·3	3·7	2·0	1·4
		Group B			
8	0·3	0·9	0·7	1·7	1·7
9	4·9	3·1	1·5	1·0	0·6
10	1·7	2·2	1·9	2·4	3·0
11	0·8	0·8	1·6	2·5	3·0
12	1·1	1·7	1·7	2·2	2·9
		Group C			
13	0·05	0·01	0·02	0·06	0·03
14	0·02	0·01	0·02	0·03	0·02
15	0·02	0·015	0·01	0·04	0·03
16	0·3	0·2	0·2	0·5	0·8
17	0·3	0·2	0·2	0·25	0·2
18	1·1	0·5	0·4	0·4	0·8
19	1·4	1·2	1·8	2·0	—
		Group D			
20	0·15	0·15	0·15	0·15	0·2
21	0·7	0·7	2·6	2·8	4·7

that in the former ones (C and D) tended to fall even lower. Values as low as 0·01 were recorded in group C. In three patients of this group, the ratio never exceeded 0·06. The cirrhotic patients without ascites, on the other hand, behaved with " Diamox " as did the normal subjects, the sodium to potassium ratio never falling below 0·6, and in most cases being well above unity. In the only Group C patient with a high sodium to potassium ratio (Number 19) the ascites was readily controlled with diuretics and sodium restriction. Malnutrition may have played a part in her illness, as she had been a vegetarian for twenty years.

Patient number 20 (Group D) also showed consistently low sodium to potassium ratios. He had had intractable ascites for three years with an undoubted partial portal vein occlusion. Liver biopsy on two occasions revealed no abnormality except that a small granuloma was seen in one specimen. He also had chronic open pulmonary tuberculosis, but repeated culture of the ascitic fluid *plus* a peritoneoscopic examination failed to support a tuberculous

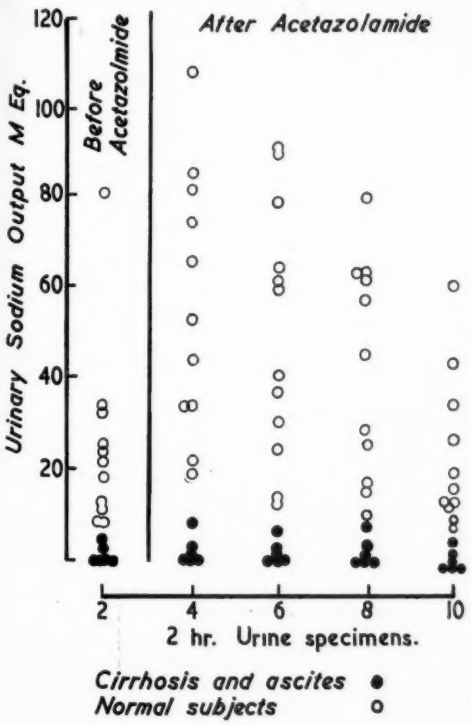

FIGURE II

Effects of acetazolamide on total sodium output

ætiology for his ascites. He behaved in every way like a cirrhotic patient with ascites, the sodium content of his urine being negligible. This patient is particularly interesting, because he illustrates the important point that liver disease, *per se*, is not a prerequisite for the secretion of a sodium-retaining factor. The other patient in this group, whose ascites was more readily controlled, showed normal sodium to potassium ratios.

The low initial sodium to potassium ratio in the ascitic groups itself suggests that something is influencing the renal tubules to retain sodium. The results during the action of "Diamox" show that this influence is not counteracted by the drug. In fact, the difference between ascitic and non-ascitic patients is, if anything, exaggerated by the administration of "Diamox" (Figure I).

The difference between the ascitic and non-ascitic groups is also well illustrated by Figure II, where the two-hourly urinary sodium outputs, both before and during the action of "Diamox", have been recorded. Six of the cirrhotic patients with ascites

TABLE IV

Comparison of Plasma Sodium Content and Twenty-four Hour Urinary Sodium Output in Cirrhotic Patients with Ascites

Subject	When Determined	Plasma Sodium Content (Milli-equivalents per Litre)	Twenty-four Hour Urinary Sodium Output (Milli-equivalents)
	Group C		
13	On admission ..	132	3·0
14	On admission ..	135	7·5
15	On admission ..	145	3·0
16	On admission ..	133	3·5
17	On admission ..	130	9·5
18	On admission ..	138	86·0
19	On admission ..	138	49·0
	Group B		
8	On admission ..	138	32·5
	Additional Patients (see text)		
E.N.	On admission ..	135	46·0
	Terminally	125	0·6
M.H.	On admission ..	138	55·0
	Terminally	115	2·75
E.H.	On admission ..	135	95·0
	Terminally	130	10·0
M.S.	On admission ..	118	0·8
	Terminally	120	0·5
J.F.	On admission ..	120	1·7
K.Z.	On admission ..	130	9·5
I.E.	On admission ..	127	1·2
R.W.	On admission ..	118	2·5

(Numbers 13 to 18) have been compared with the seven normal subjects of Group A. (Two sets of values are included for numbers 1 to 4 of this group.) The sodium output of the ascitic group is so low that there has been no overlap between the two groups.

There was a clear correlation between low plasma sodium levels and low urinary sodium outputs (Table IV, Figure III). When the plasma sodium level was within the normal range, however, the sodium output in the urine varied widely. One patient (Number 15) was of special note in that she consistently showed a very low urinary sodium output with

a high normal plasma level (145 milliequivalents per litre). This suggests that lowering of the plasma sodium level is not the primary stimulus, at least in some cases, to the secretion of the sodium-retaining factor.

As the primary action of "Diamox" is to increase excretion of bicarbonate, its efficiency as a diuretic can be judged by comparing the bicarbonate excretion in the ascitic patients (Group C) with that in the non-ascitic subjects (Groups A and B). This has been done in Table V. Administration of "Diamox" usually resulted in considerable elevation of urinary pH and bicarbonate excretion. However, it will

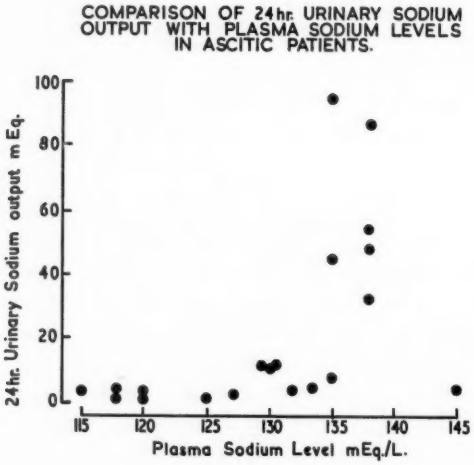

FIGURE III

be seen from the table that the average bicarbonate excretion per two-hourly period rose only to 7·7 milliequivalents in the cirrhotic patients with ascites, but to 17·6 milliequivalents in the control subjects and to 19 milliequivalents for the cirrhotic patients without ascites. This failure of "Diamox" to increase bicarbonate excretion as much in the ascitic patients as in the non-ascitic groups is paralleled by an even more remarkable difference between the groups in sodium excretion (Figure II). It will be obvious from Figure II that any significant diuretic effect of "Diamox" in the cirrhotic patients with ascites must be associated with the urinary excretion of potassium rather than sodium.

DISCUSSION

The preliminary sodium to potassium ratios in urine have been shown to be very much lower in the two ascitic groups (C and D) than in the non-ascitic ones (A and B). While in only three subjects from the latter groups does the preliminary sodium to potassium ratio fall below unity, it rises above 0·3 in only three of the former. These three subjects with ascites who did show higher preliminary sodium to potassium ratios were readily controlled, and lost their ascites rapidly on treatment with sodium restriction and mercurial diuretics. In the other six cases of ascites, the low preliminary sodium to potassium ratios were uninfluenced by the administration of

TABLE V

Bicarbonate Excretion Before and During the Action of Acetazolamide[1]

Subject	Before	During Individual Result	During Average for Group
		Group A	
1	4·45	18·5	
2	3·9	13·75	
3	14·0	18·0	17·6
4	1·0	26·25	
5	0·25	13·25	
6	1·1	22·5	
7	0·8	11·0	
		Group B	
8	2·5	20·5	
9	2·4	11·5	
10	1·8	27·5	18·8
11	0·1	15·75	
12	Not estimated		
		Group C	
13	0·1	0·85	
14	0·15	4·25	
15	0·1	9·0	7·7
16	4·5	10·1	
17	0·7	7·25	
18	2·5	8·1	
19	2·1	14·35	

[1] Results are expressed as milliequivalents per two-hour period, those during the action of acetazolamide being an average of the four consecutive two-hourly periods that were collected over the first eight hours after administration of 250 milligrammes of acetazolamide.

"Diamox". The cirrhotic patients without ascites behaved in the same manner as did the normal subjects. The higher initial sodium to potassium ratios in these groups were often even further increased by the administration of "Diamox". The only subject in those two groups to have a low preliminary ratio was Number 8 (0·3). This man had, as already mentioned, just recovered from a period during which he had been ascitic for several months.

The failure of "Diamox" to influence the urinary sodium to potassium ratio in the ascitic groups is also reflected by the similar failure of the drug to increase sodium excretion

in this group (Figure II). Normal subjects and cirrhotic patients without ascites, on the other hand, did show a significant increase in sodium excretion during the period of action of "Diamox". This was particularly apparent during the first four hours after the administration of "Diamox".

It is, perhaps, not surprising that low plasma sodium levels are invariably associated with a low twenty-four-hour urinary sodium output (Table IV, Figure III). Some such renal conservation of sodium is essential for the maintenance of stable plasma and body sodium contents. Of particular interest, however, was the wide range of urinary sodium output when the plasma sodium content was within a normal range. One patient (Number 18, Group C) with a plasma level of 138 milliequivalents per litre, excreted 86 milliequivalents of sodium in the urine in a twenty-four-hour collection period. Another, however (Number 15, Group C), with an even higher plasma level of 145 milliequivalents per litre, could excrete only three milliequivalents of sodium in twenty-four hours, despite a moderately gross ascites. Any suggestion that this may have been a hydrostatic effect on the renal vein from tense ascites was ruled out when a similar set of figures was obtained after some three litres of ascitic fluid had been removed. The inference that can be drawn from these figures is that lowering of plasma sodium level is not the only stimulus to the secretion of a potent sodium-retaining factor, and avid sodium retention by the kidney is compatible with high normal plasma levels of sodium.

It has been suggested that sodium retention occurs through defective metabolism in a diseased liver (Gordon, 1954). However, sodium retention can occur in the absence of liver disease as in Case 20 (Group D). In this case, liver disease was excluded as far as possible by two liver biopsies and a relatively normal appearance of the liver on peritoneoscopic examination. This patient did have a partial obstruction of the portal vein, and the possibility remains that alteration of the intrahepatic circulation played some part in initiating the sodium retention. However, this would seem unlikely in view of the absence of salt and water retention in the vast majority of cases of extrahepatic portal obstruction.

The results demonstrate the weak nature of "Diamox" as a diuretic in liver disease. Not only is the increase in urinary bicarbonate under the influence of "diamox" less in ascitic than in non-ascitic subjects, but, more important still, an increased urinary excretion of sodium, on which any satisfactory diuresis depends, is virtually non-existent in the ascitic group. The sodium to potassium ratio after administration of "Diamox" illustrates well the point that increased cation loss following administration of "Diamox" in many ascitic cases consists almost entirely of loss of potassium, an effect disadvantageous to the patient. Unpublished information from the manufacturers of the drug suggests, furthermore, that it is liable to precipitate hepatic coma in patients with decompensated liver disease. Counihan *et alii* (1954) point out other reasons why "Diamox" is not a good clinical diuretic. Perhaps the most important of these is the self-limiting effect of the acidosis which the drug produces.

The present experiments offer no positive light on the nature of this sodium-retaining factor in the body, which even "Diamox" fails to influence. Aldosterone (Tait *et alii*, 1952) is now known to be responsible for the mineralo-corticoid activity of the adrenals, and Luetscher and Johnson (1954) have recently extracted a substance from the urine of patients with cirrhosis of the liver which has a marked sodium-retaining activity on adrenalectomized rats, and which behaves like aldosterone on chromatographic separation. The low sodium to potassium ratios in the urine of the ascitic patients which are still further lowered by administration of "Diamox" readily fit the hypothesis that the renal tubules of these patients are under the sodium-retaining and potassium-losing effect of aldosterone (Sala and Luetscher, 1954).

Preedy and Aitken (1956) have just published three papers suggesting œstrogen excess as a possible cause of sodium and water retention in patients with cirrhosis of the liver. They based their claim on the finding of a sustained retention of salt and water in eight of nine patients suffering from cirrhosis of the liver with ascites after the daily administration of 10 milligrammes of œstradiol benzoate. They could not produce this sustained retention of salt and water either in cirrhotic patients without ascites or in patients suffering from portal hypertension without liver disease. However, they chose for their study patients with ascites who were neither rapidly gaining nor losing fluid, and in whom sodium retention was not a marked feature. Such patients are probably very sensitive to any mechanism which may affect electrolyte and water excretion. Preedy and Aitken were unable to produce maximal sodium retention by the administration of œstrogens. It is difficult, therefore, to accept from the evidence they have produced that œstrogens play any but a minor

role in the retention of sodium or water in cirrhotic patients with rapidly accumulating ascites.

If aldosterone is accepted as the principal agent responsible for the renal retention of sodium, there remains the problem of how its secretion is controlled. Evidence from these experiments suggests that high levels of circulating aldosterone may exist independently of disease of the liver or change in the plasma sodium level. Furthermore, it is now well known that its secretion is not under the direct control of the pituitary. It has been suggested that it is related to alterations in volume of some specific, but as yet unknown, part of the circulating blood compartment (Peters, 1952; Luetscher and Axelrad, 1954; Luetscher and Johnson, 1954). Perhaps the increased sodium-retaining activity in liver disease may reflect the body's effort to support a blood volume depleted by the diversion of albumin and fluid into the peritoneal cavity.

The possible importance of potassium as a regulator of aldosterone activity also remains *sub judice*. Laragh (1954) noted that potassium chloride in doses of four to twenty grammes given to patients with hypotonic extracellular fluids produced a striking increase in the plasma sodium level, although there was no definite increase in the renal excretion of sodium or water. Laragh and Stoerk (1955) concluded that variations in potassium intake exerted an important influence on sodium-retaining factors acting on the kidney. This may possibly be of considerable clinical importance, as prolonged exhibition of mercurial diuretics, together with ammonium chloride or exchange resins, in patients on a very restricted sodium intake can result in considerable body deficits of potassium, despite normal or near-normal plasma levels. Adequate supplements of potassium in such cases may be of real value.

Acknowledgements

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Proceedings of The Royal Australasian College of Physicians

ORDINARY MEETING, 1956

An ordinary meeting of the College was held in Melbourne from October 10 to 13, 1956. The President, Dr. E. G. Sayers, was in the chair.

Scientific Sessions

Three scientific sessions were held in the Lecture Hall of the Royal Australasian College of Surgeons.

W. R. Adey (Victoria) opened the first scientific session with a paper entitled "Investigations of Temporal Lobe Functions in Consciousness and Epilepsy" (written in conjunction with K. C. Bradley and Professor S. Sunderland). It was stated that the concept of a ring of cerebral cortex, the limbic ring or lobe, lying at the junctional zone between the hemisphere and the median region of the diencephalon, had been first advanced by Broca nearly eighty years previously. This lobe included many of the deep structures of the temporal lobe, such as the amygdala and hippocampus, together with overlying cortical areas forming the entorhinal area and the cingulate cortex. The relationship of activity in limbic cortex to emotional functions had been first suggested by Papez (1937), who had envisaged a series of pathways from entorhinal area and hippocampus as forming a "circuit" to the hypothalamus and thalamus, with activity reentering the entorhinal area through the cingulate cortex. While subsequent research had not borne out Papez's concept as a functional entity, the original concept had stimulated much research into the functional role of these areas of the temporal lobe. Complete bilateral temporal lobectomy in the monkey produced the syndrome of Klüver and Bucy (1939) characterized by "psychic blindness", or an inability to comprehend objects or situations in the environment, and associated with tameness, hypersexuality, omniphagia and loss of grooming habits. A more limited resection involving the amygdala was associated with hypersexuality and some degree of tameness, but Schreiner and Kling (1953) had pointed out that the latter quality in the operated animal was particularly susceptible to modification by the administration of œstrogens. While the deep structures of the temporal lobe appeared concerned in subtle modifications in the state of alerting and emotional arousal, the central tegmental regions of the mid-brain and caudal diencephalon appeared to be profoundly concerned in the process of consciousness itself. The authors' research had been directed to the study of functional interrelations between deep temporal structures and the central areas of the mid-brain. Their electrophysiological records in animals had indicated that activity was normally directed caudally from thalamus and septum through the fornix to the hippocampus and thence to the entorhinal area. Such pathways were contrary to those envisaged in the Papez circuit. The authors had shown in microelectrode studies of single cell responses in the entorhinal cortex that the cells in this cortex were greatly activated by stimulation of the fornix. They had further shown, in experimental histological and electrophysiological studies, that there were major projections from the entorhinal area to the periaqueductal grey matter of the mid-brain. Microelectrode records had indicated that cellular activity in the periaqueductal tissues was profoundly modified by entorhinal cortical stimulation. By contrast, the entorhinal cortex exerted almost no influence on more ventral regions of the tegmentum, including the zones classically described as the reticular formation. The effect of removing the entorhinal cortex had been studied in the marsupial phalanger and the baboon, and in both resulted in a significant reduction in aggressive responses to provocation. In summary, the authors' results suggested that the limbic lobe could be considered as set astride the ascencing stream of activity in the reticular areas of the brain stem at two levels—namely, at the level of the thalamus and septum rostrally, and caudally at the level of the mid-brain tegmentum—and that it was capable of modification of activity at these two levels through a series of reentrant pathways. The authors' clinical studies had been directed to the detection of focal abnormalities in the temporal lobes of children and young adults suffering from epilepsy and episodes of aggressive and asocial behaviour. Recent work had indicated the selective susceptibility of the hippocampal formation to infective, anoxic and toxic episodes during childhood. They had performed 87 electroencephalographic examinations in 66 patients, of whom 47 had been tested from Travancore Clinic in collaboration with Dr. Christine Trood. Forty-two patients had shown abnormal records. In 15 cases there had been abnormal records from the temporal lobes, six on the right, one on the left, and eight bilaterally. In two cases the focal nature of the disturbance in the non-dominant hemisphere had been considered sufficient to warrant surgical intervention, although both subjects had shown bilateral abnormal temporal records preoperatively. In both cases there had been significant post-operative improvement in the incidence of epileptic attacks. This remission had been associated with improvement in general rhythmicity of the electroencephalographic records, although in both cases there was evidence of persistent abnormal activity in the unoperated temporal lobe. Improvement in behaviour had not run parallel with the altered electroencephalographic records or diminished epileptic attacks in a period of one year since operation.

W. R. Pitney (Western Australia) presented a paper entitled "Mild Hæmophilia: A Clinical and Laboratory Study" (see page 44).

P. S. Venkatachalam (India) delivered by invitation a paper in which he considered a specific nutritional disease, kwashiorkor, affecting infants and children during late breast feeding, weaning and post-weaning

periods of life, which had been reported in recent years from various tropical countries of the world. It had recently been found by the author in New Guinea. This syndrome of protein malnutrition had been described in the literature under a variety of names with slightly differing features. Nevertheless, the condition was basically a single entity as far as ætiology, pathogenesis and pathology were concerned. Clinically, a severe case of kwashiorkor was characterized by growth failure, œdema, dyspigmentation, mental changes, gastro-intestinal symptoms, dermatosis, anæmia and various other signs associated with vitamin deficiency. The pathological changes affecting the various organs and the biochemical alterations observed in the blood and body fluids were characteristic. Treatment was the rapid provision of easily assimilable proteins in the form of milk. The possibility of preventing and eradicating this serious condition lay in the judicious use of available food materials in the tropics to the best nutritional advantage.

Bryan Hudson (Victoria) continued the session with a paper entitled "The Nature of the Pigmentary Disorder in Addison's Disease" (to be published in a later issue of AUSTRALASIAN ANNALS OF MEDICINE).

B. S. HETZEL (South Australia) closed the session with a paper entitled "Comparison of the Early Metabolic Effects of Triiodothyronine and Hydrocortisone in Man" (in conjunction with H. Lander). He said that previous studies had disclosed changes suggestive of increased protein and fat catabolism during certain emotionally stressful experiences in man. In order to investigate the mechanisms underlying these changes, studies of the early effects of triiodothyronine and hydrocortisone had been carried out in healthy volunteer medical students. Observations had been made of serum and urinary electrolytes, urea, inorganic phosphate and serum lipid fractions following intravenous administration of triiodothyronine (0·5 and 1·0 milligramme) and hydrocortisone (50 milligrammes) by infusion in normal saline over four hours. The results had been compared with levels following the infusion of saline alone. Triiodothyronine had produced significant elevation in serum inorganic phosphate level in eight hours, but no change in serum urea, sodium, potassium, phospholipids or fatty acid levels. Hydrocortisone had produced a significant elevation in serum inorganic phosphate level in eight hours, and in serum cholesterol level in six hours, but no change in serum urea, sodium, fatty acid or phospholipid levels. Triiodothyronine had produced significant elevation of inorganic phosphorus excretion with slight increase in urea and total nitrogen excretion. Hydrocortisone had produced a transient increase followed by a decrease in urea, total nitrogen and sodium excretion associated with similar changes in urine flow, but a marked increase in potassium excretion had been observed. It was concluded that triiodothyronine increased phosphate breakdown and fat catabolism within eight hours, while hydrocortisone mobilized intracellular fluid containing potassium and phosphate, but was not catabolic in this dosage. The resemblance of these patterns to those already observed under conditions of stress in man suggested that the thyroid might be involved in their mechanism.

Ewen Downie (Victoria) opened the second scientific session with a contribution entitled "The Treatment of Diabetic Patients with Sulphonylurea Compounds", which summarized the work of Joseph Bornstein, Bryan Hudson and himself in this field over the previous nine months. After reviewing the findings of workers in other countries, he proceeded to give details of the response of 27 patients to BZ-55 ("Carbutamide"). The patients were a selected group, and in general their response was in line with the findings of other workers in this field. He then compared the action of BZ-55 with that of insulin and indicated that in no sense could "Carbutamide" be considered as a substitute for insulin. After considering the various theories suggested to explain its mode of action, he pointed out that Dr. Bornstein had recently demonstrated an inhibition of transamination. That was apparently specific for this group of drugs and was not shown by other sulphonamides. The effect of such inhibition, if continued indefinitely, was unknown, but it was suggested that for the time being the sulphonylureas should be used only under strict supervision and should not be made generally available at present.

Professor L. J. Witts (Oxford), by invitation, addressed the College on the subject of "Research and the Patient".

Robert Hecker (South Australia) concluded the session with a paper dealing with "The Mechanism of Sodium Retention in Cirrhosis of the Liver with Ascites: the Effect of Acetazolamide on Urinary Electrolytes" (see page 75).

A. J. Barnett (Victoria) opened the third scientific session with a contribution entitled "Raynaud's Phenomenon and Scleroderma", in which he considered their mutual relationship from an analysis of 15 patients showing both these features. Using as criteria whether or not the patient's illness was typical Raynaud's disease and the extent of the scleroderma, he showed that the cases could be classified into four groups: (*a*) clinical Raynaud's disease, later scleroderma of hands; (*b*) clinical Raynaud's disease, later widespread scleroderma; (*c*) not typical Raynaud's disease, scleroderma of hands; (*d*) not typical) Raynaud's disease, widespread scleroderma. Group (*a* corresponded to "secondary scleroderma"; group (*b*) to "acrosclerosis"; group (*d*) to "diffuse systemic sclerosis" as used generally. There was an overlap of clinical features found in groups (*a*), (*b*) and (*d*), and it was suggested that they were variants of the same underlying condition. Group (*c*) seemed to behave differently, in that the scleroderma remained localized to the hands, and there was no tendency for visceral involvement. In scleroderma associated with Raynaud's phenomenon, there was evidence for some structural abnormality of the digital vessels—delayed flushing of the finger-tips following an arterial occlusion reactive hyperæmia test in most cases and low heat elimination following reflex heating.

H. R. Gilmore (South Australia) delivered a paper entitled "The Effect of Protamine Sulphate on Alimentary Lipæmia in Normal and Atherosclerotic Males" (written in conjunction with A. J. Day, C. R. Schwartz and Gwendoline K. Wilkinson), in which he referred to nine male patients who had been given a standard fat meal in the fasting state, and who had recovered from a previous myocardial infarction at least three months previously. The effect of 0·1 gramme of protamine sulphate given intravenously two and a half hours after the standard meal had been followed by quarter-hour sampling of blood until the end of three hours. This procedure had been repeated on the same patients, a similar volume of normal saline being used. Two control groups of nine individuals each had been similarly investigated, both protamine sulphate and saline being used. One was a group of men who were of similar age to the atherosclerotic patients, but in whom there was no clinical evidence of atherosclerosis or hypertension. The other consisted of young male student volunteers. The sera were assessed for content of cholesterol

fatty acids, phospholipids and turbidity. A significant difference in level of those substances had been noted only in the total esterified fatty acids. In the young male volunteers the protamine sulphate had caused a significant rise. Both the atherosclerotic and age control males had shown a small rise in total esterified fatty acids, which was, however, significantly smaller than that for the young male volunteers. The difference, it was concluded, reflected an effect of aging in the human male.

Ian R. Mackay (Victoria) delivered a paper on " The Clinical Features and Significance of Macroglobulinæmia " (see AUSTRALASIAN ANNALS OF MEDICINE, **5** (4), 244, 1956).

Bruce King (Victoria) (in conjunction with W. E. King) presented by invitation a paper entitled " Some Observations on the Liver in Congestive Cardiac Failure ".

R. J. Sawers (Victoria) closed the session with a contribution on " The Genetics of Some Hæmorrhagic Diseases ". In discussing the genetics of three types of hæmorrhagic disease, emphasis was directed to the diagnostic, prognostic and eugenic implications which were derived from clinical and laboratory study. The hæmophilias were discussed in detail ; the data used were based on a survey in the Victorian population in which the birth incidence was shown to be one in 5000 male births. It was concluded that 50% of hæmophiliacs lacked a history of the disease in prior generations ; 70% of such subjects suffered complete deficiency of α or β-prothromboplastin and therefore suffered the disease in the expected severe degree. In the majority of instances the mothers of such subjects were thought to be true genetic carriers of the disease (due to recent mutation), and this indicated that they and their daughters should be warned of the likelihood of their bearing affected children. The second hæmorrhagic condition which was discussed was a severe one due to an intrinsic defect of thrombocytes. Ordinarily the condition (Glannzmann's disease) was due to inheritance of a dominant gene. Three pedigrees were described in which the affected children were the offspring of first cousins. The absence of the disease in the parents and the type of marriage union indicated that the disease in these families resulted from inheritance of two recessive genes. Further intermarriage within or between these families should be warned against. The third condition discussed was the usually mild but common condition apparently due to vascular fragility (von Willebrand's disease ; " pseudo-hæmophilia "). The importance of the condition lay in the occasional severe hæmorrhage which followed surgery and tooth extraction. It was due to inheritance of a dominant somatic gene, and a family history was present in 70% of cases. The diagnosis depended on finding prolonged skin bleeding times and/or reduced capillary resistance, and on a positive family history. The prognosis was good in all but the occasional case, when bleeding might be unexpectedly severe. No eugenic warning appeared indicated.

CLINICAL MEETING

A clinical meeting was held at the Alfred Hospital, Commercial Road, Prahran. Alfred Bardsley, in demonstrating " Familial Hyperlipæmia ", presented a case history of a man aged thirty years. The patient had complained of recurring attacks of severe upper abdominal pain for a period of ten years. This pain had been attributed at various times to renal colic, gall-bladder disease and functional dyspepsia. Finally, a diagnosis of relapsing pancreatitis was considered, and investigations revealed a gross degree of hyperlipæmia. The only relevant clinical findings consisted of splenomegaly and xanthomatous skin lesions. In addition there was long-standing albuminuria with no other evidence of renal disease. Biopsies were performed—bone marrow, skin lesions and the kidney. The examination of marrow showed normal hæmopoietic tissue and also the presence of considerable numbers of foamy lipoid storage cells. The skin lesion was typical of cutaneous xanthomatosis, but the kidney biopsy showed only minor non-specific changes. Investigations of serum of the patient's parents revealed an abnormally high cholesterol level in the mother. The case was considered to be an example of essential hyperlipæmia, and the general features of this condition were discussed, particularly in relation to the diagnosis and clinical features. The attacks of pain in this case were considered to be due to relapsing pancreatitis, which was a well recognized complication of the condition. Persistent albuminuria had not been previously reported in essential hyperlipæmia, and the possible significance of that was discussed, but it was felt that on the evidence no firm conclusions could be reached at the present stage.

J. J. Billings and Kevin O'Day, F.R.A.C.S., demonstrated a case of " Refsum's Syndrome—Heredopathia Atactica Polyneuritiformis " in a man, aged twenty-one years, who had first presented a few months earlier with the complaint of sudden onset of deafness and ataxia. Clinical examination had revealed very severe bilateral deafness and an ichthyotic condition of the skin which had been present from birth. An associated congenital lesion was a curious deformity of the third and fourth toes of both feet due to short metatarsals. There were irregular pigment collections in the *fundi oculi*, and the patient admitted on questioning that during the past five years he had noticed some gradual failure of vision, particularly at night. The visual field showed concentric narrowing, and Dr. Kevin O'Day considered that the condition was atypical *retinitis pigmentosa*. The patient was admitted to St. Vincent's Hospital for more detailed investigation. A quite unexpected abnormality was found in the cerebro-spinal fluid. There was a marked increase in the protein content to 140 milligrammes per 100 millilitres, whilst the cell count was zero. A week later the protein content had risen to 400 milligrammes per 100 millilitres. In 1945, Refsum of the University of Oslo described a syndrome consisting of atypical *retinitis pigmentosa*, nerve deafness, ichthyotic skin changes, congenital deformities of the hands and feet, polyneuritis, cerebellar ataxia, greatly raised cerebrospinal fluid protein content with albumino-cytological dissociation and death from cardiac failure. The skeletal deformities, deafness and ichthyosis have not been constant features in the adult patients. Refsum termed the syndrome *heredopathia atactica polyneuritiformis* to indicate its hereditary character and two of its most prominent clinical features, the ataxia and the polyneuritis. During the few weeks since his admission to hospital the patient's condition had deteriorated rapidly, and the remaining clinical features described by Refsum had appeared. He now complained of numbness of the tips of the fingers and toes,

there was wasting and weakness of the limbs, especially the legs, the tendon reflexes had disappeared, and there was slight peripheral loss of sensation in the limbs with tenderness of the calf muscles. There was pronounced ataxia, much more severe than the polyneuritis could account for. Most serious of all was the appearance of cardiac failure with dilatation of the heart and pulmonary congestion. The cardiac failure was partially relieved by the administration of digitalis and " Neptal ", but the blood pressure was co sistently low (70 to 80 millimetres of mercury). The electrocardiogram showed a left heart strain pattern, and a more recent record showed a nodal rhythm associated with the strain pattern. The syndrome was essentially a familial one resulting from the marriage of blood relations. Refsum had altogether described six cases in adults and four in children. One case had been reported by Clark and Critchley in London and one by Reese and Bareta from the Mayo Clinic. The present case appeared to be the thirteenth case to be described and the first recognized in Australia, and was only the second in which the parents had not been related. The high incidence of consanguineous marriages amongst parents of the affected individuals was strong evidence in favour of recessive heredity. With intermarriage, both marriage partners might be heterozygous carriers with the gene for a particular disease in a single dose. Under those conditions, according to the Mendelian laws, one-fourth of the offspring had a chance of receiving a double dose of the pathological gene and thus became affected with the disease. The condition being considered therefore was probably caused by a single autosomal (non-sex-linked) recessive gene.

Dr. Kevin O'Day demonstrated the histological changes in *retinitis pigmentosa*. He referred to the association of the condition with various other neurological disorders.

Morris C. Davis presented two patients with " Advanced Renal Failure Presenting Interesting Clinical Features ", and made a plea for a reclassification of renal disease in the light of these cases and others from a very large personal series.

A. J. Barnett, Bryan Hudson and J. Bornstein presented a case of " Aldosteronism (Conn's Syndrome) ".

G. E. RENNIE MEMORIAL LECTURE

The G. E. Rennie Memorial Lecture for 1956 was delivered by Dr. E. L. Susman (New South Wales) on Friday, October 12, 1956, at 2.15 p.m. in the Lecture Hall of the Royal Australasian College of Surgeons, under the title of " The Neurology of Chronic Alcoholism ".

ANNIE B. CUNNING LECTURE ON NUTRITION

The ninth Annie B. Cunning Lecture on Nutrition was delivered in the Public Lecture Theatre in the University of Melbourne on the evening of Thursday, October 11. The lecture was delivered by Mr. P. G. Law, M.Sc., F.Inst.P., leader of the Australian Antarctic Research Expedition, on the subject " Nutrition in the Antarctic " (to be published in *The Medical Journal of Australia*). The lecture was attended by an audience of 500 persons, and guests were later entertained at supper in the Union House.

MEMBERSHIP

Admission of Members. The following candidates who were successful at an examination held in Australia in September-October, 1956, were admitted to Membership on October 9, 1956: N. D. Abbot, R. G. Gold and P. M. Last, of South Australia; C. W. Baird, R. H. D. Bean, J. L. Blunt, W. H. Orchard, A. C. L. Clark and R. K. Doig, of Victoria; C. S. H. Reed, D. E. Smith and N. J. Yorkston, of New South Wales; D. D. Letham, of Western Australia; A. G. Zaver, of Queensland.

Obituary. Council regards with regret the death of Sir Wilberforce Newton, of Victoria, and Dr. R. R. Bye, of New South Wales, who were Fellows, and of Dr. M. F. Deck and Dr. C. B. Hudson, of New South Wales, who were Members of the College.

Membership Roll. The College now has a roll of 318 Fellows and 496 Members.

GENERAL

Election of Member Councillor. Dr. Bryan Hudson, of Victoria, was elected by Council to the casual vacancy in the position of Member Councillor created by the retirement of Dr. H. W. Garlick upon his election to Fellowship. Dr. Hudson will hold office until the annual meeting in 1957.

Scholarships. Two Wunderly Travelling Scholarships in Thoracic Diseases were awarded for the year 1957. The recipients were Dr. J. D. Sinclair, of Auckland, New Zealand, and Dr. D. H. Meyers, of Victoria. The Travelling Scholarship in Medicine and the Allied Sciences for 1957 was awarded to Dr. Lyal Watson, of New South Wales.

Representatives of the College. The following have been appointed as College representatives: L. E. Hurley, on the Medical and Scientific Committee to the Anti-Cancer Council of Victoria, and H. Maynard Rennie, to the Board of Directors of Prince Henry Hospital, Sydney.

Joint Advisory Committee with the Royal Australasian College of Surgeons. A Joint Advisory Committee has been set up by the Council of the College and the Council of the Royal Australasian College of Surgeons to confer on matters of mutual interest to both Colleges. The College will be represented on this committee by the following panel of representatives: Dr. Clive

Fitts, Dr. J. G. Hayden, Dr. C. G. McDonald and Dr. H. Maynard Rennie.

Future Meetings of the College. The annual meeting in 1957 will be held in Brisbane from May 28. The ordinary meeting will be held in Sydney from October 15 to 19.

Research Grants. Grants from the Research Fund of the College for the year 1957 have been made to Dr. J. Margolis, at the Nuffield Institute for Medical Research, Oxford; to Dr. B. P. Billington, at the Department of Medicine of the University of Sydney; to Dr. V. M. Hercus and to Dr. R. G. Epps, at the Unit of Clinical Investigation at the Royal North Shore Hospital; to Dr. B. G. Firkin, at the Clinical Research Unit of the Royal Prince Alfred Hospital, Sydney; and to Dr. J. B. Stokes, at the Department of Hæmatology, Royal Perth Hospital.

Research Advisory Committee. Council has appointed Sir Macfarlane Burnet, of Victoria, and Professor C. R. B. Blackburn, of New South Wales, to the Research Advisory Committee of the College.

CORRIGENDUM

IN the article entitled "Treatment of Severe Arterial Hypertension: Results from Long-Term Use of Methonium Compounds with and without the Addition of Reserpine", by A. J. Barnett, in the issue of November, 1956, the photographs for Figure IIIA and Figure IIIC, on page 282, have unfortunately been interchanged. This makes it appear as if the heart size in the patient H.F. had increased, instead of decreased, the latter of course being the true state of affairs. We regret this error.

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